ALESSANDRA FERREIRA BARBOSA LEE

Avaliação da função executiva e da fluência verbal em pacientes com doença de Parkinson

Dissertação apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção de título de Mestre em Ciências

Programa de Ciências da Reabilitação

Orientadora: Profa. Dra. Letícia Lessa Mansur

Coorientadora: Profa. Dra. Mariana Callil Voos

SÃO PAULO

2018

ALESSANDRA FERREIRA BARBOSA LEE

Avaliação da função executiva e da fluência verbal em pacientes com doença de Parkinson

Dissertação apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção de título de Mestre em Ciências

Programa de Ciências da Reabilitação

Orientadora: Profa. Dra. Letícia Lessa Mansur

Coorientadora Profa. Dra. Mariana Callil Voos

SÃO PAULO

2018

Dados Internacionais de Catalogação na Publicação (CIP)

Preparada pela Biblioteca da
Faculdade de Medicina da Universidade de São Paulo

Lee, Alessandra Ferreira Barbosa
Avaliação da função executiva e da fluência verbal em pacientes com doença de Parkinson / Alessandra Ferreira Barbosa Lee. -- São Paulo, 2018.
Dissertação(mestrado)--Faculdade de Medicina da Universidade de São Paulo.
Programa de Ciências da Reabilitação.
Orientadora: Letícia Lessa Mansur.
Coorientadora: Mariana Callil Voos.

Descritores: 1.Doença de Parkinson 2.Cognição 3.Envelhecimento 4.Função executiva 5.Transtornos dos movimentos 6.Gânglios da base

USP/FM/DBD-016/18

DEDICATÓRIA

Essa dissertação é dedicada a todos os pacientes com Parkinson e seus familiares que enfrentam uma batalha diária desde o momento do diagnóstico. Todos os esforços de nós pesquisadores pouco vale comparado ao de vocês.

Dedico também aos colegas fisioterapeutas, como forma de incentivo, principalmente aos recém-formados, a buscarem sempre pelo conhecimento e pela formação.

AGRADECIMENTOS

À Profa. Dra. Letícia Lessa Mansur, pelo acolhimento que permitiu a minha entrada nesse programa de pós-graduação. Serei eternamente grata pela sua disponibilidade e sua contribuição que foram essenciais para a conclusão desse mestrado.

À Profa. Dra. Mariana Callil Voos, por ser além de mestra, uma inspiração e uma amiga para toda a vida. Foram seus conselhos, seu profissionalismo e seu empenho pela ciência que me incentivaram, desde a faculdade, a crescer como profissional e como acadêmica. Obrigada por me guiar, ouvir, incentivar e respeitar meus momentos.

Às companheiras do REMOVE, grupo de estudos em reabilitação nos distúrbios do movimento, Dra. Hsin Fen Chien, Dra. Carolina Souza, fisioterapeutas Janini Chen e Débora Valente Francato. Obrigada por toda ajuda na avaliação dos pacientes, análises estatísticas e discussões dos resultados.

Às grandes fisioterapeutas, pesquisadoras e amigas que pude fazer ao longo desse trajeto, por serem um respiro de alegria, diversão e calmaria. Obrigada Graziela Polido, Mariana Artilheiro, Joyce Martini, Janini Chen e Mariene Simões.

Ao meu amado marido, Rafael, por ter me acompanhado nesse período de mestrado com muito amor e paciência, me incentivando a trabalhar quando eu desanimava, sem jamais me pressionar. Obrigada pelo carinho de todos os dias. Obrigada por confiar em mim.

Ao meus pais que tanto batalharam e contribuíram para a minha formação pessoal e profissional. Obrigada, pai, por me inspirar a estudar, por me dar o gosto pelo conhecimento. Obrigada, mãe, por me dar o equilíbrio, me ensinar a ser leve. Impossível agradecer completamente por tanto amor, tanta confiança e tanta amizade. Vocês sempre serão meu porto seguro.

A Deus, pela vida e por ser como sou, por todas as oportunidades que me dá todos os dias e pela força nos momentos de dificuldade. “És tu Senhor, meu único bem”.

“Ah, tem uma repetição, que sempre outras vezes em minha vida acontece. Eu atravesso as coisas – e no meio da travessia não vejo! – só estava era entretido na ideia dos lugares de saída e de chegada. Assaz o senhor sabe: a gente quer passar um rio a nado, e passa; mas vai dar na outra banda é num ponto muito mais em baixo, bem diverso do em que primeiro se pensou. Viver nem não é muito perigoso?”

Grande Sertão: Veredas
João Guimarães Rosa

NORMALIZAÇÃO ADOTADA

Esta Tese está de acordo com as seguintes normas, em vigor no momento desta publicação:

Referências: adaptado de *International Committee of Medical Journals Editors* (Vancouver).

Universidade de São Paulo. Faculdade de Medicina. Divisão de Biblioteca e Documentação. *Guia de apresentação de dissertações, teses e monografias*. Elaborado por Anneliese Carneiro da Cunha, Maria Julia de A. L. Freddi, Maria F. Crestana, Marinalva de Souza Aragão, Suely Campos Cardoso, Valéria Vilhena. 3a ed. São Paulo: Divisão de Biblioteca e Documentação; 2011.

Abreviaturas dos títulos dos periódicos de acordo com *List of Journals Indexed in Index Medicus*.

SUMÁRIO

Lee AFB. *Avaliação da função executiva e da fluência verbal em pacientes com doença de Parkinson* [Dissertação]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2018.

Pacientes com doença de Parkinson (DP) apresentam diversos sintomas não motores, dentre eles, alterações cognitivas. Déficits de função executiva podem ser observados desde os estágios iniciais da DP e impactam na independência funcional e na qualidade de vida. A função executiva é essencial para a realização de atividades de vida diária, que requerem integração cognitivo-motora. A realização de atividades cotidianas depende não só do sistema motor, mas também da interpretação e do processamento sensorial/ perceptual e da seleção e do planejamento da melhor estratégia motora. Sendo assim, um grande número de atividades de vida diária pode ser afetado por déficits na função executiva em pacientes com DP. Nessas tarefas, os componentes cognitivos e motores competem por recursos atencionais, o que pode prejudicar o desempenho em um ou em ambos os componentes. Entretanto, os estudos são muito direcionados para a análise de tarefas-duplas que envolvam equilíbrio em ortostatismo e marcha, mas contemplam pouco outras tarefas motoras. Os objetivos desse estudo foram (1) comparar o desempenho de pacientes com DP com o de um grupo controle nos testes de função executiva (*Trail Making Test)* e de fluência verbal (fluência semântica e fonêmica e diadococinesia oral /pataka/) e (2) investigar possíveis correlações entre função executiva e fluência verbal. O estudo foi realizado de maneira transversal, em uma única sessão, em uma avaliação de cerca de 50 minutos. Quarenta pacientes com DP (idade entre 50 e 79 anos, Hoehn & Yahr entre 2 e 3) e quarenta controles (com idade e escolaridade semelhantes) foram avaliados com o *Trail Making Test*, a fluência verbal semântica e fonêmica e o teste de diadococinesia oral. Na parte A do TMT, os participantes conectaram círculos numerados de 1 a 25, em sequência. Na parte B, os participantes conectaram círculos alternando números e letras (1-A-2-B-3-C-4-D-5-E-6-F-7-G-8-H-9-I-10-J-11-K-12-L-13). No teste de fluência verbal fonêmica, foi solicitado que os participantes dissessem palavras começando com a letra F. No teste de fluência verbal semântica, os participantes disseram o maior número de animais possível, em 60 segundos. No teste de diadococinesia oral, os participantes repetiram a sequência /pataka/ o mais rápido possível. Os grupos foram comparados por meio de análises de variância e as relações entre as variáveis foram investigadas pelo teste de correlação de Pearson. A análise de variância mostrou diferenças significativas entre grupos ($F_{1,78}$=10,55; p=0,002) e entre partes do *Trail Making Test* ($F_{1,78}$=154,02; p<0,001). A parte B apresentou tempos maiores que a parte A (p<0,001). Pacientes com DP disseram menos palavras nos testes de fluência verbal, em comparação aos controles (p<0,001). Pacientes com DP repetiram a sequência /pataka/ menos vezes que os controles (p=0,019). Houve forte correlação entre o teste de fluência verbal fonêmica e a parte B do *Trail Making Test* (valor de r=-0,874 e p=0,001) e entre a diadococinesia oral e as partes A e B do *Trail Making Test* (valor de r=-0,824 e p=0,001). A correlação entre a parte B do *Trail Making Test,* que é uma medida de função executiva e reflete a habilidade de integração cognitivo-motora e as tarefas de fluência verbal, evidencia a importância do controle motor para as tarefas de fala. A tarefa da fala fornece não somente sobrecarga cognitiva, mas também motora para pacientes com DP. Esse conhecimento é importante para a prática clínica, uma vez que é necessário detectar a natureza do acometimento e da tarefa para usá-las de maneira adequada em programas de reabilitação.

Descritores: doença de Parkinson; cognição; envelhecimento; função executiva; transtornos dos movimentos; gânglios da base

Lee AFB. *Assessment of executive function and verbal fluency in patients with Parkinson´s Disease* [Dissertation]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2018.

Patients with Parkinson´s disease (PD) can present several non-motor symptoms, including cognitive deficits. Executive function deficits can be observed since the early stages of PD and impact on functional independence and quality of life. The executive function is essential to the activities of daily living, which require cognitive-motor integration. The performance of activities of daily living depends not only on the motor system, but also on the sensory/ perceptual interpretation and processing and the selection and planning of the best motor strategy. Therefore, many activities of daily living can be affected by deficits in the executive function in patients with PD. In such tasks, cognitive and motor components compete for attentional resources, which may impair the performance of one or both tasks. However, most studies focus on to the analysis of dual-tasks involving orthostatic balance and gait, but they do not approach other motor tasks. The objectives of this study were (1) to compare the performance of patients with PD with a control group in executive function (Trail Making Test) and verbal fluency tests (semantic and phonemic and oral diadochokinesis /pataka/) and (2) to investigate possible correlations between executive function and verbal fluency. This was a cross-sectional study and the tests were performed individually in a 50-minute single session. Forty people with PD (aged 50 - 79 years, Hoehn & Yahr 2 - 3) and forty controls (with similar age and education) were evaluated with Trail Making Test (TMT, executive function), phonemic/semantic verbal fluency and oral diadochokinesis (/pataka/) tests. In part A of Trail Making Test, participants connected circles with the numbers 1-25, in sequence. In part B, participants connected circles in a sequence with alternated numbers and letters (1-A-2-B-3-C-4-D-5-E-6-F-7-G-8-H-9-I-10-J-11-K-12-L-13). In the phonemic verbal fluency test, participants were instructed to say words beginning with the letter F. In the semantic verbal fluency test, participants were instructed to say out loud as many animals as they could remember, in 60 seconds. In the oral diadochokinesis test, participants were asked to say the /pataka/ sequence as fast as they could. Groups were compared by analyses of variance and the relationships between the variables were investigated by Pearson correlation tests. Analysis of variance showed significant differences between groups ($F_{1,78}$=10.55; p=0.002) and between Trail Making Test parts ($F_{1,78}$=154.02; p<0.001). Part B showed longer times than part A (p<0.001). People with PD said fewer words in both fluency tests, compared to controls (p<0.001). People with PD repeated the sequence /pataka/ less times than controls (p=0.019). There was a strong correlation between the phonemic verbal fluency test and the part B of Trail Making Test (r=-0.874 and p=0.001) and between the oral diadochokinesis test and both parts of the Trail Making Test (r=-0.824 e p=0.001). The correlation between the part B of Trail Making Test, which is an executive function measure and reflects the cognitive-motor integration ability, and the verbal fluency tests, evidences the importance of motor control for speech tasks. Speech tasks not only provide cognitive overload, but also motor overload in patients with PD. This knowledge is important in clinical practice, in which therapists must detect the nature of the disability and the task to use this information properly in rehabilitation programs.

Descriptors: Parkinson disease; cognition; aging; executive function; movement disorders; basal ganglia

1. APRESENTAÇÃO

O estudo do controle motor é algo que me instiga desde a graduação. Realizei meu projeto de Iniciação Científica, apoiado pela FAPESP, sobre avaliação postural por meio da posturografia estática e dinâmica, de mulheres com hipertrofia mamária, orientado pela Profa. Dra. Clarice Tanaka de 2009 a 2010. Entre 2010 e 2011 trabalhei com avaliação do equilíbrio no aprimoramento e entre 2012 e 2013 acompanhei avaliações e discussões científicas de pesquisadores e pós-graduandos na área de Distúrbios do Movimento e surgiu o desejo de realizar o mestrado.

Em parceria com o Ambulatório de Distúrbios do Movimento do Departamento de Neurologia do Hospital das Clínicas da Faculdade de Medicina da USP, iniciei a investigação do efeito de perturbações sensoriais e cognitivas sobre o equilíbrio estático de pacientes com doença de Parkinson (DP), sob a orientação da Profa. Dra. Mariana Callil Voos, em 2014. Verificamos que os pacientes com DP apresentavam maior deslocamento e velocidade de oscilação na posturografia estática sem perturbação (com olhos abertos). Essa oscilação aumentava com os olhos fechados, porém era ainda mais expressiva quando uma tarefa cognitiva era adicionada. Os achados confirmaram que mesmo em tarefas mais simples do que a marcha, como manter-se em ortostatismo sem apoio, já existia a competição por recursos atencionais. O trabalho denominado *"The competition with a concurrent cognitive task disrupted posturographic measures in Parkinson´s Disease"* (PD) foi publicado na revista Arquivos de Neuro-Psiquiatria em 2015, volume 73, fascículo 11, páginas 906-912 (Anexo 1). Resultados parciais foram apresentados na forma de pôster na 6ª Reunião do Departamento Científico de Transtornos do Movimento da Associação Brasileira de Neurologia, em 2015

("Interação sensório-cognitivo-motora no equilíbrio postural de pacientes com DP", Anexo 2). Também realizamos o artigo de revisão "*Gait, posture and cognition in PD*" publicado na revista *Dementia & Neuropsychologia* em 2016, que explorou a influência da cognição e da escolaridade no controle motor de pacientes com DP e suas implicações clínicas (Anexo 3).

Fui apresentada pela Profa. Dra. Mariana Callil Voos (co-orientadora) à Profa. Dra. Letícia Lessa Mansur (orientadora) e tive a oportunidade de ministrar a aula "Aprendizagem motora: idade adulta e envelhecimento" na disciplina MFT0809 – Bases conceituais da fala entre 2014 e 2017. A Profa. Dra. Letícia Lessa Mansur abriu as portas para um novo campo: o controle motor envolvido na produção da fala. Tanto na fisioterapia, quanto na fonoaudiologia (e nas demais áreas da saúde), o envolvimento dos sistemas sensoriais e cognitivos no controle do movimento tem sido foco de diversos estudos. Nos pacientes com DP, o envolvimento do sistema cognitivo no controle motor também tem sido investigado por meio de tarefas-duplas. Nessas tarefas, há competição por recursos atencionais e muitos estudos estão focados na perturbação que a tarefa cognitiva causa no equilíbrio dinâmico e na marcha. Há poucos estudos que avaliam essa interação cognitivo-motora em movimentos de membros superiores.

Ingressei no programa "Ciências da Reabilitação" em setembro de 2015. Incluímos no nosso protocolo de avaliação ferramentas amplamente utilizadas, como o teste de Fluência Verbal (Anexo 4) e o *Trail Making Test* (Anexo 5), que permitiram avaliar o desempenho cognitivo-motor em pacientes com DP em tarefas envolvendo fala e destreza manual. O projeto de pesquisa foi submetido e aprovado pela Plataforma Brasil, sob o parecer número 1.631.497 (Anexo 6). Resultados parciais desse estudo foram apresentados em 2016 no *20th International Congress of PD and Movement*

Disorders e publicados nos anais do evento, da *Movement Disorders* (Anexo 7) e no formato de pôster no XXVII Congresso Brasileiro de Neurologia (Anexo 8).

Os resultados finais foram apresentados, em formato de pôster, na 7ª Reunião do Departamento Científico de Transtornos do Movimento da Associação Brasileira de Neurologia, em agosto de 2017 (Anexo 9) e o trabalho completo, intitulado *"Cognitive or cognitive-motor executive function tasks? Evaluating verbal fluency measures in people with PD"* foi aceito para publicação em julho de 2017 (Anexo 10), pela revista *BioMed Research International,* indexada pelo Medline, fator de impacto 2.476. A proposta desse estudo foi aprofundar o conhecimento atual a respeito do desempenho de pacientes com DP em tarefa-dupla. Atualmente, os protocolos de avaliação de tarefas-duplas estão bastante focados em tarefas de equilíbrio e de locomoção. O presente estudo visou discutir o desempenho em testes de destreza manual e fluência verbal, que também demandam a realização concomitante de tarefas motoras e cognitivas.

Essa dissertação foi redigida de acordo com as normas de editoração da Faculdade de Medicina da Universidade de São Paulo (Programa Ciências da Reabilitação). A revisão de literatura, a análise crítica e a conclusão são apresentadas em inglês. O artigo com os resultados principais é apresentado na íntegra, no corpo do trabalho. O projeto de pesquisa, com a respectiva aprovação da Plataforma Brasil, é apresentado em anexo. Outros artigos relevantes publicados durante a realização desse projeto são apresentados em anexo.

2. LITERATURE REVIEW

The populational ageing is a phenomenon observed in several developing countries, including Brazil (Carvalho & Rodriguez-Wong, 2008). As the population gets older, a higher incidence of chronic and degenerative diseases, as Parkinson's disease (PD), can be observed (Blum et al., 2001). PD is a neurodegenerative disease, described in 1817 by James Parkinson (Parkinson, 2002; Jankovic, 2008), characterized by several motor symptoms, with the classic symptoms being resting tremor, muscular rigidity, bradykinesia and postural instability (Jankovic, 2008). PD is not uncommon in the adult population, but the incidence increases in the elderly, affecting 1.5 to 2.0% of the population over 60 years (Brienesse & Emerson, 2013). In a study about the Brazilian population, the incidence of PD reached 3.4% of people above 64 years (Barbosa et al., 2006). The impact of PD on quality of life encourages the development of research for better understanding the physiopathology and management (Klein et al., 2010; Cruise et al., 2011; Lawson et al., 2014).

Besides the classic signs of PD, other motor and non-motor symptoms are frequent. In a multicenter study by Barone et al. (2009), a semi-structured interview evaluated 1072 patients and 98.6% reported non-motor symptoms. Even patients in the early stages of PD commonly have some cognitive symptoms, such as memory impairment, attention, visuospatial or executive function deficits. According to Litvan et al. (2011), up to 80% of patients with PD develop dementia.

One factor that increases the rate of evolution to dementia is the presence of deficits in the executive function (Levy et al., 2002; Hanna-Pladdy, 2007). The executive function involves environmental adaptation, such as establishing and maintaining goals, generating plans and alternating them, monitoring internal and external information, suppressing inappropriate behaviors, solving problems, inhibiting, initiating and sequencing actions (Hanna-Pladdy, 2007). The frontal lobe is highly involved in the executive functions (Owen, 2004; Janvin et al., 2006; Hanna-Pladdy, 2007; Mills et al., 2016). The death of dopaminergic neurons in the substantia nigra diminishes the activation of the caudate nucleus that stops stimulating the lateral dorsal frontal lobe (Bohnen et al., 2003; Owen, 2004; Bohnen et al., 2015). Consequently, patients experience difficulty in problems solving and in actions planning (Lawson et al., 2014).

A review published by our group (Barbosa et al., 2016) explained the interactions between balance and gait disorders with cognitive deficits in PD. We argued that not only motor performance, but also sensory and perceptual processing and motor planning were affected by PD. Therefore, in dynamic activities, such as walking, these deficits contributed to balance deficits, pathological changes in gait parameters (such as freezing episodes) and falls. The association of another activity, either cognitive or motor can impair postural control and gait performance, since it overloads the central processing capacity, limiting the production of motor responses in patients with PD (Stegemoller et al., 2014). The executive dysfunction is associated to the decline in cognitive-motor performance and causes a major impact on quality of life (Stegemoller et al., 2014; Jacobs et al., 2014). Cognitive-motor performance is essential in daily life activities and patients with PD often have a decline in functional independence, because the motor component of the dual-task is affected when the cognitive demand increases. This discussion has been focused towards the impact of the additional cognitive task on gait and balance (Bloem et al., 2006; Brauer & Morris, 2010; Jacobs et al., 2014; Strouwen et al., 2016). However, little is known about cognitive-motor interference (Pashler, 1994; Voos et al., 2015) in dual-tasks involving upper limbs and speech motor control.

Therefore, this study explored executive function (Levy et al., 2002; Hanna-Pladdy, 2007) and speech clinical assessment (Gurd, 2000; Shapiro et al., 2005; McDowd et al., 2011). The executive function test was the Trail Making Test. It is a paper and pencil test that consists in drawing a trail to match numbers in sequence (Part A) and number and letters alternately (Part B). The time spent in part A reflects motor performance. Part B requires mental flexibility, task switching, response inhibition and working memory and evaluates cognitive-motor dual-task performance (Souza et al., 2013). TMT delta (time in part B – time in part A) is considered as a pure cognitive measure, because it isolates the cognitive impact added by alternating the letters sequence (Souza et al., 2013).

Verbal fluency tests are recommended for cognitive screening in people with PD. Although methods vary (Gurd, 2000; Shapiro et al., 2005; McDowd et al., 2011), participants are usually instructed to say as many words as possible, in 60 seconds. In the phonemic test, words must begin with a determined letter (e.g. letter F). In the semantic test, words must belong to the same category (e.g. animals). Most studies only interpret the score on fluency tests as a pure cognitive measure and do not consider the motor demands involved in words emission. Speech evaluation protocols also include the oral diadochokinesis tests, which consist on rapid repetition of a syllable or syllable sequences, as quickly as possible (e.g. */pataka/*) (Wyliea et al., 2009; Padovani, Gielow & Behlau, 2009). The decrease in the syllable production rate can be related to motor control, and speed reduction may be associated to words intelligibility.

2.1. OBJECTIVES AND HYPOTHESES

This study aimed to describe the performance of patients with PD, compared to controls, on executive function (Trail Making Test) and verbal fluency (phonemic/semantic and oral diadochokinesia) and to investigate possible relationships between these measures.

Verbal fluency tests are cognitive-motor, because they involve phonarticulatory coordination, response inhibition and phonological processing. Therefore, we hypothesized that the performance on verbal fluency tests would show higher correlation with part B of Trail Making Test (which is also a cognitive-motor measure), than with part A of Trail Making Test (which is a motor measure of upper limb coordination) and delta of Trail Making Test (which is a cognitive measure).

Oral diadochokinesia is considered a motor coordination evaluation of speech production. Therefore, we hypothesized that oral diadochokinesia would show higher correlations with part A of Trail Making Test (motor measure of upper limb coordination), than with part B of Trail Making Test (cognitive-motor measure) or delta of Trail Making Test (cognitive measure).

2.2. RELEVANCE

This study fills a gap in the literature regarding the upper limb (e.g. writing) and speech cognitive-motor assessment in PD. It is well known that cognitive-motor interference occurs in balance and gait tasks, but few studies explored other types of motor task. The functional and socioeconomic impact of falls and the multifactorial nature of postural control have received attention of the scientific community, although other motor tasks, which depend on the same mechanisms, have been poorly explored.

The Trail Making Test is a way of evaluating executive functions, but the upper limb motor component might have been neglected and is affected by PD. Patients with PD show performance disruption due to the competition between cognitive and motor tasks performed at the same time. Therefore, instead of analyzing exclusively the delta of Trail Making Test, which is considered a pure cognitive measure, we also focused on parts A and B, which reflect the motor and cognitive-motor performance, respectively.

The knowledge about cognitive-motor interaction is relevant in the assessment of activities of daily living, such as speaking and writing. Cognitive and motor deficits may have impact on the functional independence and quality of life of patients with PD. Question regarding cognitive-motor interactions, such as "What is being evaluated when I ask the patient to walk while saying the months of the year, or when holding a tray?", "Which systems are being overloaded? Does the perturbation involve motor or cognitive overload?" may help optimizing evaluation protocols for PD.

3. ARTIGO PRINCIPAL

COGNITIVE OR COGNITIVE-MOTOR EXECUTIVE FUNCTION TASK? EVALUATING VERBAL FLUENCY MEASURES IN PATIENTS WITH PARKINSON'S DISEASE

Objetivo: Descrever o desempenho de pacientes com DP nos testes de fluência verbal semântica, fonêmica, na diadococinesia oral e em um teste de função executiva (Trail Making Test) e investigar se essas medidas estão relacionadas.

Periódico: *BioMed Research International*

Fator de impacto 2015: 2.476

Data de submissão: 19/04/2017

Data de aceite: 18/07/2017

Data de publicação: 20/08/2017

Cognitive or cognitive-motor executive function task? Evaluating verbal fluency measures in patients with Parkinson's disease

Alessandra Ferreira Barbosa[1,2]; Mariana Callil Voos[1,2]; Janini Chen[2,3]; Debora Cristina Valente Francato[2,3]; Carolina de Oliveira Souza[2,3]; Egberto Reis Barbosa[3]; Hsin Fen Chien[2,3]; Letícia Lessa Mansur[1]

1. Physical Therapy, Occupational Therapy and Speech Therapy Department, University of São Paulo, School of Medicine, São Paulo, Brazil.

2. ReMove. Rehabilitation in Movement Disorders Research Group.

3. Movement Disorders Clinic, Department of Neurology, Clinics Hospital of University of São Paulo, School of Medicine, São Paulo, Brazil.

Corresponding author:

Alessandra Ferreira Barbosa (alefbar@gmail.com)

R Cipotânea, 51, 2º andar

05360-000 Cidade Universitária São Paulo, SP, Brazil

Conflicts of interest: All authors declare no conflicts of interest

Source of funding: No funding to declare

ABSTRACT

Introduction: Executive function deficits are observed in people with Parkinson disease (PD) since early stages and have great impact on daily living activities. Verbal fluency and oral diadochokinesia involve phonarticulatory coordination, response inhibition and phonological processing and may also be affected in people with PD. This study aimed to describe the performance of people with PD and an age- and education-matched control group on executive function, phonemic/semantic verbal fluency and oral diadochokinesia tests and to investigate possible relationships between them. **Methods:** Forty people with PD and forty controls were evaluated with Trail Making Test (TMT, executive function), phonemic/semantic verbal fluency and oral diadochokinesia (/pataka/) tests. Groups were compared by ANOVA and relationships were investigated by Pearson tests. **Results:** People with PD showed longer times in parts A and B of TMT. They also said fewer words in phonemic/semantic verbal fluency tests and less syllables in the diadochokinesia test, compared to controls. Oral diadochokinesia strongly correlated to parts A and B of TMT and to phonemic verbal fluency. **Conclusion:** Oral diadochokinesia was correlated to executive function and verbal fluency. The cognitive-motor interaction in verbal fluency and oral diadochokinesia must be considered not to overestimate the cognitive or motor impairments in people with PD.

Keywords: Parkinson disease, cognition, verbal fluency disorders, executive function

1. INTRODUCTION

People with Parkinson disease (PD) experience non-motor symptoms, such as attention/memory deficits and visuospatial disorganization [1]. Executive function plays an important role in these aspects and involves mental flexibility, decision making, problem solving, motor sequencing/inhibiting and task switching [2]. The efficiency in daily living activities relies on the integrity of executive function and deficits can be found even in PD early stages [3].

The incidence of mild cognitive impairment reaches 19-38% of people with PD [2] and may cause disability in self-caring, driving and interacting [4] and increased falls risk [5,6]. Executive function depends on frontal structures, which are impaired in people with PD, due to dopamine depletion in nigrostriatal projections [1,7]. Deficits in executive function can be attributed to the reduced activity in the caudate nucleus, even in people without dementia [8].

Cortical cholinergic denervation is associated with cognitive decline in people with PD. Bohenen et al. (2015) investigated the relationship between cognitive function and imaging analysis [9]. They concluded that dopaminergic caudate nucleus denervation is frequent in people with mild cognitive impairment. Cognitive impairment progresses as cholinergic denervation increases. They also reported that the cholinergic system is probably overactivated in the initial phase of mild cognitive impairment, as a compensatory mechanism for dopaminergic denervation.

Several tests can be used to evaluate executive function, e.g. Trail Making Test (TMT) and verbal fluency tests. TMT consists in drawing a trail to match numbers in sequence (Part A) and number and letters alternately (Part B). The time spent in part A reflects motor performance. Part B requires mental flexibility, task switching, response inhibition and working memory and evaluates cognitive-motor dual-task performance [10]. TMT delta (time in part B – time in part A) is considered as a pure cognitive measure, because it isolates the cognitive impact added by alternating the letters sequence [10].

Verbal fluency tests are recommended for cognitive screening in people with PD. Although methods may vary [11,12], participants are usually instructed to say as many words as possible, in 60 seconds. In the phonemic test, words must begin with a determined letter. In the semantic test, words must belong to the same category. Most studies only interpret the score on fluency tests as a cognitive measure and do not consider the task motor demands. As people get older, speech production can be impaired. This loss can be attributed to a reduction in muscular strength, endurance and coordination, which are intensified by PD [13].

Speech evaluation protocols include oral diadochokinesia tests, which consist on rapid repetition of a syllable or syllable sequences, as quickly as possible [14]. The decrease in the syllable production rate can be related to motor control, and speed reduction may be associated to maintaining intelligibility [15].

Verbal fluency tests can be considered cognitive-motor tasks. They involve phonarticulatory coordination, response inhibition and phonological processing. Therefore, we hypothesized that the performance on verbal fluency would show higher correlation with part B of TMT (which is also a cognitive-motor measure), than with part A of TMT (motor measure) and delta TMT (cognitive measure). We also hypothesized that oral diadochokinesia would show higher correlations with part A of TMT (motor measure), than with part B of TMT (cognitive-motor measure) or delta of

TMT (cognitive measure). This study aimed to describe the performance of people with PD, compared with an age- and education-matched control group, on executive function, phonemic/semantic verbal fluency and oral diadochokinesia and to investigate possible relationships between these measures, due to cognitive-motor interactions.

2. METHOD

This study was approved by the Committee on Research Ethics at Clinics Hospital of University of São Paulo (process 1.631.497). All participants read and signed the written informed consent.

2.1 Participants

Seventy-eight outpatients with idiopathic PD, from the Movement Disorders Clinic of Clinics Hospital were invited to participate in the experimental group. Fifty-two volunteered and forty met inclusion criteria. Seven were excluded because they were in the early stage of the disease (Hoehn & Yahr score below 2). Five were excluded because they were adapting to recent changes on medications. Fifty-nine healthy older adults from a senior center of University of São Paulo were invited to participate in the control group. Forty-five volunteered and forty met inclusion criteria. Four controls were excluded for having less than four years of formal education. One control was excluded due to having a neurological condition.

People aged 50-79 years, with four or more years of formal education and Mini-Mental State Examination score above 23 [16] were included. Additional inclusion criteria for patients with PD were having received the diagnosis of PD according to the

United Kingdom Parkinson Disease Society Brain Bank criteria [17]; Hoehn & Yahr [18] score 2-3; and optimized daily dosage of antiparkinsonian drug treatment during the last four weeks prior to study entry. People with PD were on their best “on” state during assessment. Volunteers with acute/terminal illnesses, myocardial infarction in the last six months, moderate/severe chronic obstructive pulmonary disease and neurological and/or muscular diseases (evaluated by self-report) were excluded.

Demographic data from both groups are described in Table 1.

2.2 Assessment

Participants were assessed individually in a fifty minute-session. The initial anamnesis consisted of collecting demographic/screening information (age, number of years of formal education, Mini-Mental State Examination, motor section of Unified Parkinson Disease Rating Scale [17]). Then, participants were assessed with TMT, phonemic/semantic verbal fluency test and oral diadochokinesia test. Tests were performed in random order to avoid learning effects. Participants were comfortably seated on a desk during evaluation.

In part A of TMT, participants connected circles with the numbers 1-25, in sequence. In part B, participants connected circles in a sequence with alternated numbers and letters (1-A-2-B-3-C-4-D-5-E-6-F-7-G-8-H-9-I-10-J-11-K-12-L-13). When errors occurred, the examiner said that there was an error and asked the participant to return to the last correct circle. The scores were the duration taken to complete each part. The test was interrupted if not completed within 300 seconds, and the highest possible score (300) was given [10].

In the phonemic verbal fluency test, participants were instructed to say words beginning with the letter F. In the semantic verbal fluency test, participants were instructed to say out loud as many animals as they could remember, in 60 seconds. Scores were calculated by counting the number of words. Repeated words were scored only once and derived words were excluded [14].

In the oral diadochokinesia test, participants were asked to say the /pataka/ sequence as fast as they could. The emission was recorded and analyzed in Praat software (publicly available on web). The variable syllables/second was based on the number of syllables emitted in the first eight seconds.

2.3 Statistical analysis

Data showed normal distribution (tested by Kolmogorov-Smirnov). Student T tests compared age and years of formal education of PD and control groups. Chi-square tests investigated sex distribution differences. Analyses of variance (ANOVA) were performed to compare executive function, verbal fluency and oral diadochokinesia (considered as dependent variables) of both groups.

Pearson correlation tests examined possible correlations between executive function, verbal fluency and oral diadochokinesia in PD group. Coefficients higher than 0.799 were considered as strong and coefficients between 0.400 and 0.799 were considered as moderate [19]. Fisher test was used to compare correlation coefficients. In all tests, the level of significance was set at alpha<0.05.

3. RESULTS

Demographic characteristics are displayed in Table 1. The groups did not significantly differ in age, gender, years of formal education and Mini-mental State Examination scores (Table 1). Fifteen participants were classified as Hoehn & Yahr 2, twelve as 2.5 and thirteen as 3.

Table 1: Demographic data.

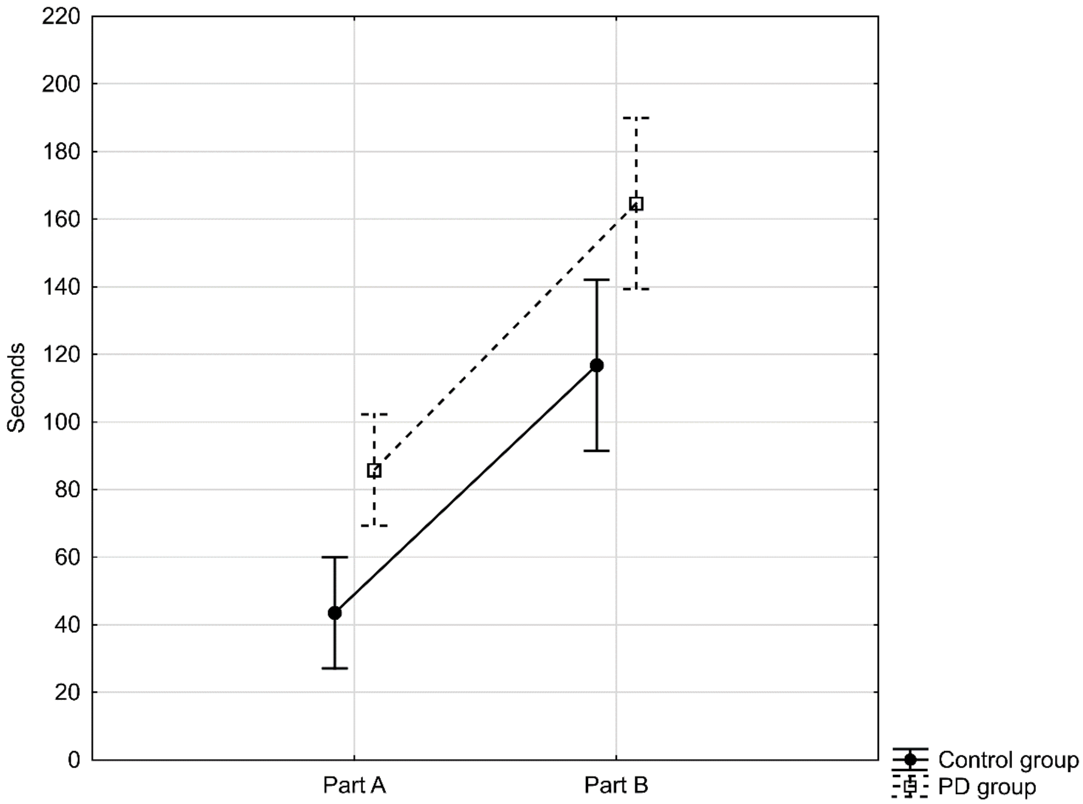
Groups	People with PD	Controls	P value
Age (years)	67.2±4.3	67.0±7.9	0.472
Education (years)	9.8±4.9	11.2±4.5	0.088
Gender (F/M)	24/16	27/13	0.485
Mini Mental State Examination score	27.7±2.1	27.8±1.3	0.290
Disease duration (years)	9.3±6.1	-	-
UPDRS III	27.9±12.0	-	-

PD: Parkinson disease; UPDRS III: Unified Parkinson Disease Rating Scale [17].

Trail Making Test

People with PD needed more time to complete parts A and B of TMT than controls. ANOVA showed significant differences between groups ($F_{1,78}$=10.55; p=0.002) and between TMT parts ($F_{1,78}$=154.02; p<0.001). Part B showed longer times than part A. TMT delta did not significantly differ between the groups (p=0.855). No interaction between groups and parts was observed ($F_{1,78}$=0.20; p=0.652) (Figure 1).

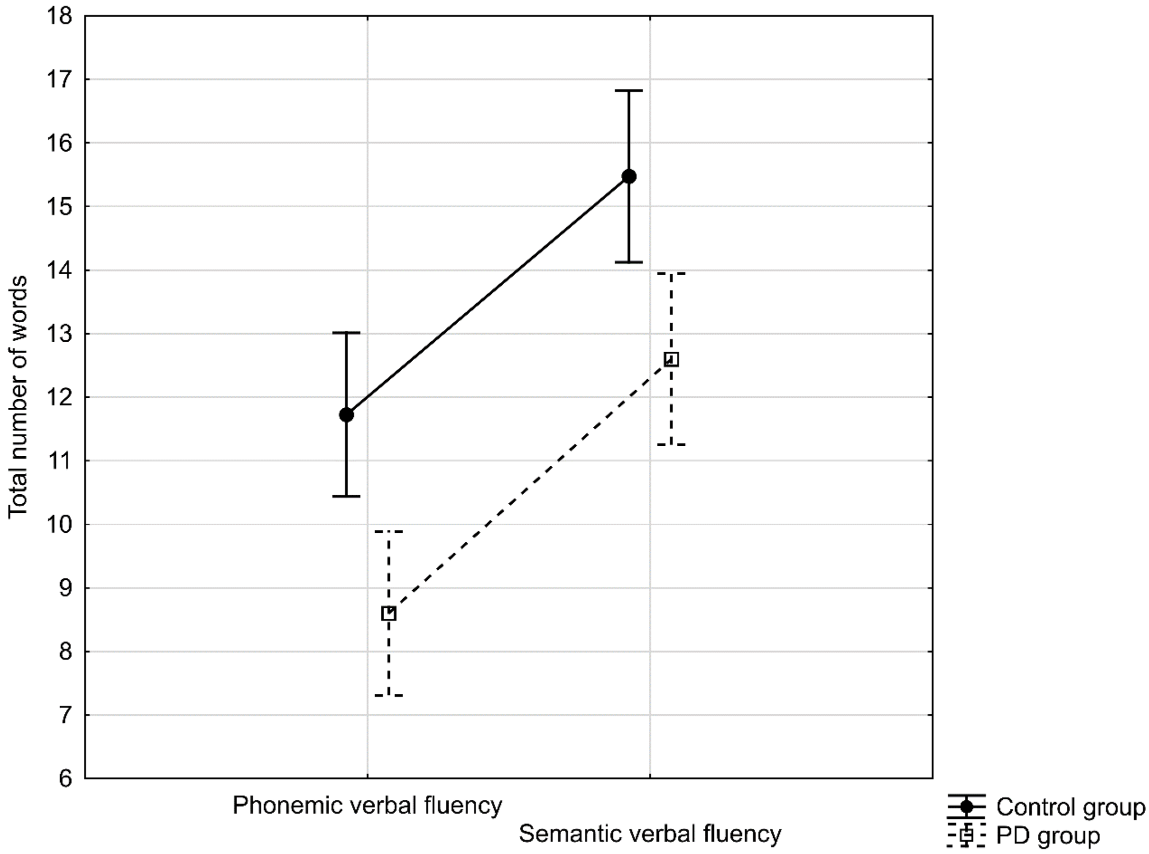
Figure 1: Performance on parts A and B of Trail Making Test (TMT)



Verbal fluency tests

People with PD said fewer words in both fluency tests, compared to controls. ANOVA showed a significant difference between groups ($F_{1,78}$=12.98; p<0.001). People with PD group said fewer words in the phonemic fluency than in the semantic fluency test. ANOVA showed a significant difference between fluency tests (phonemic or semantic) ($F_{1,78}$=81.23; p<0.001). No interaction between groups and tests was observed (($F_{1,78}$=0.84; p=0.772) (Figure 2).

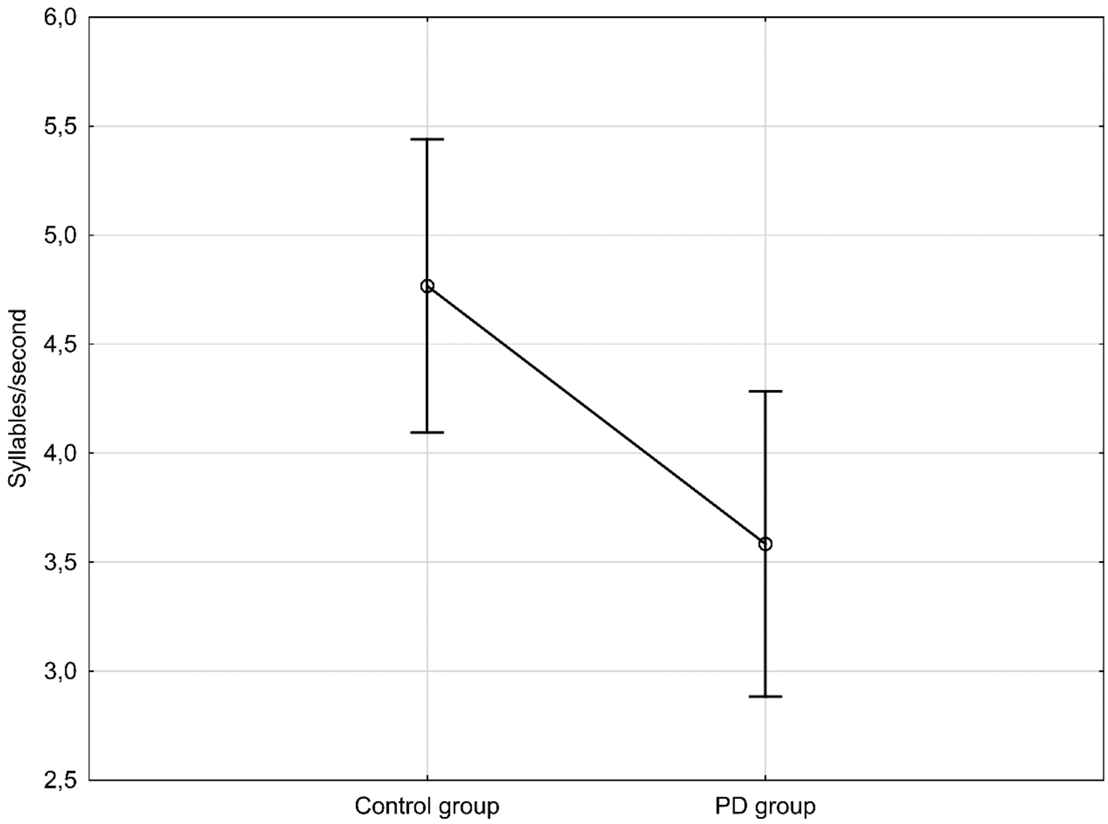
Figure 2: Performance on phonemic and semantic verbal fluency tests



Oral diadochokinesia test

People with PD repeated the sequence /pataka/ less times than controls ($F_{1,23}$=6.36; p=0.019) in 8 seconds (Figure 3).

Figure 3: Performance on oral diadochokinesia test



Correlation analysis

Pearson correlation tests investigated possible relationships between the times on part A, B and delta of TMT, the number of words said on phonemic/semantic verbal fluency tests and the number of syllables repetitions in oral diadochokinesia test. The correlations are displayed in Table 2. Moderate to strong correlations were found between TMT, phonemic verbal fluency and oral diadochokinesia (Table 2).

Table 2: Correlations between executive function (parts A, B and delta of Trail Making Test), phonemic/semantic verbal fluency and oral diadochokinesia scores in people with Parkinson disease (Pearson correlation coefficients).

	Part A (TMT)	Part B (TMT)	Delta (TMT)	Oral diadochokinesia
Phonemic verbal fluency test	r= -0.712 p= 0.009*	r= -0.874 p= 0.001*	r= -0.740 p= 0.006*	r= 0.684 p= 0.014*
Semantic verbal fluency test	r= -0.311 p= 0.325	r= -0.468 p= 0.125	r= -0.339 p= 0.281	r= 0.325 p= 0.303
Oral diadochokinesia	r= -0.838 p= 0.001*	r= -0.824 p= 0.001*	r= -0.689 p= 0.013*	-----

*p<0.05; TMT: Trail Making Test

The correlation coefficients were compared by Fisher test and they are displayed in Table 3. The correlation between part B of TMT and phonemic verbal fluency was significantly stronger than the correlation between part A of TMT and phonemic verbal fluency (p=0.050). The correlations between parts A and B of TMT and oral diadochokinesia were significantly stronger than the correlation between delta of TMT and oral diadochokinesia (p=0.011 and p=0.018, respectively) (Table 3).

Table 3: Comparison between correlation coefficients (Fisher tests).

	Part B X phonemic verbal fluency (r=-0.874)	**TMT delta X phonemic verbal fluency (r=-0.740)**
Part A X phonemic verbal fluency (r=-0.712)	0.050*	0.780
TMT delta X phonemic verbal fluency (r=-0.740)	0.100	---------
	Part B X Diadochokinesia test (r=-0.824)	**TMT delta X Diadochokinesia test (r=-0.689)**
Part A X Diadochokinesia test (r=-0.838)	0.850	0.011*
Part B X Diadochokinesia test (r=-0.824)	---------	0.018*

*p<0.05

4. DISCUSSION

The present study compared the performance of people with PD with a control group on executive function, phonemic/semantic verbal fluency and oral diadochokinesia.

People with PD showed more difficulty on TMT than controls. Both PD and control groups showed poorer performance in part B of TMT, compared to part A. Part A evaluates motor speed and coordination. Part B requires the same motor control, but demands more complex cognitive skills (mental flexibility, visual scanning, response inhibition) [10]. Part B of TMT can detect mild cognitive impairment in people with PD [23] and predict difficulties in instrumental activities of daily living [24].

In the verbal fluency test, people with PD said fewer words than controls, especially in the phonemic test. Previous studies showed that the phonemic verbal fluency was impaired in people with PD, due to the association between substantia nigra volume and phonemic verbal fluency [20]. Besides, as nouns are stored by temporal lobe neurons, the semantic verbal fluency would be more affected in people with temporal lobe lesions, e.g. Alzheimer's disease [21], than in people with PD. People with PD show a higher preservation of semantic content pathways and usually rely on semantic cues to facilitate lexical search [22]. In the present study, both groups showed better performance on semantic verbal fluency. Although verbal fluency can be affected in people with a low educational status or mild cognitive impairment, animals' names are one of the easiest semantic categories. People are exposed to this kind of information since childhood, which can explain our findings.

People with PD said less syllables/second than controls in oral diadochokinesia. In dual-tasks with motor and cognitive demands, patients with PD have difficulty in both components (e.g. gait [23], alternating steps [24]). This can also be observed in oral diadochokinesia. Another possible explanation would be the difficulty of patients with PD to find a speed-accuracy trade-off in repetition tasks of sequences, as in /pataka/. The speed may have been prioritized over the accuracy [28]. People with PD who are pressing for performance speed may have taken longer to resolve the interference (for instance differentiate /pa/ vs /ta/ vs /ka/) that arises from the activation of an unintended response.

The present study investigated the relationships between executive function, verbal fluency and oral diadochokinesia. We hypothesized that verbal fluency performance would show higher correlation with part B of TMT (which is also a cognitive-motor measure), than with part A of TMT (motor measure) and delta TMT (cognitive measure). A strong correlation between phonemic verbal fluency and part B of TMT was found. Both phonemic verbal fluency and executive function are related to caudate nucleus circuitry integrity [1,20]. Dopamine depletion in the basal ganglia affects the main connections with the frontal lobe and compromises the activation of two major regions of projection: premotor areas (e.g. supplementary motor area, responsible for motor planning) and frontal lobe dorsal and ventral regions (involved in cognitive abilities) [1]. Semantic processing involves the activation of cortical areas (including motor areas) and depends on the engagement of the left frontal cortex [25,26]. When the neural projections to all these cortical areas are lesioned, people with PD may show difficulties in motor planning and semantic processing.

We expected the correlation between the phonemic verbal fluency and part B of TMT to be the strongest and this hypothesis was confirmed. The Fisher test showed that the correlation between part B of TMT and phonemic verbal fluency was significantly higher than the correlations between phonemic verbal fluency and the other scores of TMT (part A and delta). The strong correlation between part B of TMT and phonemic verbal fluency suggests that dual-task performance is important in both tasks. The motor components of tracing the trail (part B of TMT) and speaking (phonemic verbal fluency) may be competing for resources that would be allocated exclusively to the cognitive components (e.g. following the sequence in part B of TMT and recalling the words in phonemic verbal fluency).

Few studies consider that, besides reflecting cognitive impairment, verbal fluency is also influenced by motor control [11,22]. Verbal fluency demands motor coordination, speed, misspelled words inhibition and mental flexibility for word selection. Interestingly, the semantic verbal fluency did not show the same correlation with part B of TMT. This finding agrees with Gurd (2000) [27], who showed that the motor component did not affect semantic and phonemic fluency tasks in the same way. Therefore, semantic and phonemic tasks should be combined in the evaluation of people with PD, because they show distinct levels of difficulty. PD and control groups showed better performance in the semantic fluency test. This fact can explain why semantic fluency scores did not correlate to other variables.

We hypothesized that oral diadochokinesia would show higher correlations with part A of TMT (motor measure), than with part B (cognitive-motor measure) and delta of TMT (cognitive measure). Diadochokinesia scores were strongly correlated to part A of TMT and to phonemic verbal fluency scores. This correlation was expected, since both tests measure motor speed. Part A of TMT is influenced by motor coordination and verbal fluency depends on quickly producing syllables.

The correlation between oral diadochokinesia and part B of TMT was strong, contradicting our hypothesis. The correlations between oral diadochokinesia and parts A and B of TMT were significantly higher than the correlation with TMT delta. However, correlation coefficients were not significantly different when compared to each other by Fisher test. Therefore, oral diadochokinesia (with /pataka/ syllables) cannot be considered an exclusively motor task. Oral diadochokinesia is a cognitive-motor task. The switching syllables from /pa/ to /ta/, from /ta/ to /ka/ and from /ka/ to /pa/ involves not only motor control, but also inhibition control, task switching and sequencing, as part B of TMT. Also, in tasks demanding speed and accuracy, people with PD tend to have poor accuracy when asked to focus on speed which can be attributed to the flaw on inhibitory control [28]. These facts also explain the moderate correlation between oral diadochokinesia and TMT delta, which is a cognitive measure.

The present study shows that the cognitive and motor interference that can be observed in complex tasks as gait and balance [29,30] can also be observed in verbal fluency and oral diadochokinesia. Our findings amplify the knowledge of dual-task paradigm in people with PD: cognitive-motor interference also occurs in speech production (verbal fluency and oral diadochokinesia) and paper and pencil tests (TMT).

These new facts lead to reflections on how to interpret the results of verbal fluency and oral diadochokinesia. It is important to consider that cognitive and motor overload may be caused when multiple cognitive and motor components are performed simultaneously. The increase on cognitive-motor demands can impair postural stability and gait in PD [31]. Therefore, the positioning (sitting vs. standing) during verbal fluency or oral diadochokinesia assessment may also influence the results, as standing require higher motor control than sitting. If the motor aspects of cognitive-motor tasks are not fully considered, cognitive impairment can be overestimated in people with PD.

We must mention that only moderately affected participants were evaluated, (Hoehn & Yahr 2-3; 27 classified as 2 and 2.5). Therefore, it is important to note that these analyzes cannot be generalized to all PD severities. We used TMT as the executive function measure, but there are other tests that can be used for more detailed cognitive assessment. We used words with F and animals as phonemic and semantic verbal fluency measures, but there are other tests that can be used for more detailed verbal fluency evaluation. Many PD and control participants had low educational status (mean: 10.5 years of formal education). Education affects the performance on all tasks of the present study [32,33]. Future studies should investigate the influence of PD severity and education on executive function, verbal fluency and oral diadochokinesia. Although groups did not have significant differences between age and education, future studies should pair PD and control volunteers by age and education.

5. CONCLUSION

People with PD showed more difficulty than controls in executive function, semantic and phonemic verbal fluency and oral diadochokinesia. Parts A and B of TMT correlated to phonemic verbal fluency and to oral diadochokinesia. This cognitive-motor interaction in verbal fluency and oral diadochokinesia must be considered not to overestimate the cognitive or motor impairments in people with PD.

REFERENCES

[1] A.M. Owen, Cognitive dysfunction in Parkinson disease: The role of frontostriatal circuitry, Neuroscientist 10(6) (2004) 525-537.

[2] I. Litvan, D. Aarsland, C.H. Adler, J.G. Goldman, J. Kulisevsky, B. Mollenhauer, M.C. Rodriguez-Oroz, A.I. Troester, D. Weintraub, MDS Task Force on Mild Cognitive Impairment in Parkinson's Disease: Critical Review of PD-MCI, Movement Disorders 26(10) (2011) 1814-1824.

[3] B. Hanna-Pladdy, Dysexecutive Syndromes in Neurologic Disease, Journal of Neurologic Physical Therapy 31(3) (2007) 119-127.

[4] M. Ranchet, E. Broussolle, A. Poisson, L. Paire-Ficout, Relationships between Cognitive Functions and Driving Behavior in Parkinson's Disease, European Neurology 68(2) (2012) 98-107.

[5] M. Amboni, P. Barone, J.M. Hausdorff, Cognitive Contributions to Gait and Falls: Evidence and Implications, Movement Disorders 28(11) (2013) 1520-1533.

[6] C.d.O. Souza, M.C. Voos, D.V. Francato, H.F. Chien, E.R. Barbosa, Influence of Educational Status on Executive Function and Functional Balance in Individuals with Parkinson Disease, Cognitive and Behavioral Neurology 26(1) (2013) 6-13.

[7] S. Tekin, J.L. Cummings, Frontal-subcortical neuronal circuits and clinical neuropsychiatry - An update, Journal of Psychosomatic Research 53(2) (2002) 647-654.

[8] O. Monchi, M. Petrides, B. Mejia-Constain, A.P. Strafella, Cortical activity in Parkinson's disease during executive processing depends on striatal involvement, Brain 130 (2007) 233-244.

[9] N. Bohnen, R. Albin, M. Müller, M. Petrou, V. Kotagal, R. Koeppe, P. Scott, Frequency of cholinergic and caudate nucleus dopaminergic deficits across the

predemented cognitive spectrum of Parkinson disease and evidence of interaction effects, JAMA Neurol, 72(2) (2015) 194-200.

[10] C.R. Bowie, P.D. Harvey, Administration and interpretation of the trail making test, Nature Protocols 1(5) (2006) 2277-2281.

[11] I.T. Rodrigues, J.J. Ferreira, M. Coelho, M.M. Rosa, A. Castro-Caldas, Action verbal fluency in Parkinson's patients, Arquivos De Neuro-Psiquiatria 73(6) (2015) 520-525.

[12] V. Varalta, A. Picelli, C. Fonte, S. Amato, C. Melotti, V. Zatezalo, L. Saltuari, N. Smania, Relationship between Cognitive Performance and Motor Dysfunction in Patients with Parkinson's Disease: A Pilot Cross-Sectional Study, Biomed Research International (2015).

[13] V.d.O. Martins, C.R.F.d. Andrade, Perfil evolutivo da fluência da fala de falantes do português brasileiro, Pró-Fono Revista de Atualização Científica 20(1) (2008) 7-12.

[14] M.D. Lezak, D.B. Howieson, D.W. Loring, Neuropsychological assessment, Oxford University Press, New York, New York, 2004, p. 1016.

[15] M. Padovani, I. Gielow, M. Behlau, Phonarticulatory diadochokinesis in young and elderly individuals, Arquivos De Neuro-Psiquiatria 67(1) (2009) 58-61.

[16] S.M.D. Brucki, R. Nitrini, P. Caramelli, P.H.F. Bertolucci, I.H. Okamoto, Suggestions for utilization of the mini-mental state examination in Brazil, Arquivos De Neuro-Psiquiatria 61(3B) (2003) 777-781.

[17] L.V. Metman, B. Myre, N. Verwey, S. Hassin-Baer, J. Arzbaecher, D. Sierens, R. Bakay, Test-retest reliability of UPDRS-III, dyskinesia scales, and timed motor tests in patients with advanced Parkinson's disease: An argument against multiple baseline assessments, Movement Disorders 19(9) (2004) 1079-1084.

[18] M.M. Hoehn, M.D. Yahr, Parkinsonism: onset, progression, and mortality (Reprinted from Neurology, vol 17, 1967), Neurology 57(10) (2001) S11-S26.

[19] M. Mukaka, A guide to appropriate use of Correlation coefficient in medical research, Malawi Med J. 24(3) (2012) 69–71.

[20] U. Ellfolk, J. Joutsa, J.O. Rinne, R. Parkkola, P. Jokinen, M. Karrasch, Striatal volume is related to phonemic verbal fluency but not to semantic or alternating verbal fluency in early Parkinson's disease, Journal of Neural Transmission 121(1) (2014) 33-40.

[21] K.A. Shapiro, F.M. Mottaghy, N.O. Schiller, T.D. Poeppel, M.O. Fluss, H.W. Muller, A. Caramazza, B.J. Krause, Dissociating neural correlates for nouns and verbs, Neuroimage 24(4) (2005) 1058-1067.

[22] J. McDowd, L. Hoffman, E. Rozek, K.E. Lyons, R. Pahwa, J. Burns, S. Kemper, Understanding Verbal Fluency in Healthy Aging, Alzheimer's Disease, and Parkinson's Disease, Neuropsychology 25(2) (2011) 210-225.

[23] R. Biundo, L. Weis, S. Facchini, P. Formento-Dojot, A. Vallelunga, M. Pilleri, A. Antonini, Cognitive profiling of Parkinson disease patients with mild cognitive impairment and dementia, Parkinsonism & Related Disorders 20(4) (2014) 394-399.

[24] C.I. Higginson, K. Lanni, K.A. Sigvardt, E.A. Disbrow, The contribution of trail making to the prediction of performance-based instrumental activities of daily living in Parkinson's disease without dementia, Journal of Clinical and Experimental Neuropsychology 35(5) (2013) 530-539.

[25] J. Binder, R. Desai, The neurobiology of semantic memory, Trends in Cognitive Sciences, 15(11) (2011) 527;36.

[26] S. Ketteler, D. Ketteler, R. Vohn, F. Kastrau, J. Schulz, K. Reetz, W. Huber, The processing of lexical ambiguity in healthy ageing and Parkinson′s disease: Role of cortico-subcortical networks, Brain Research, 1581 (2014) 51-63.

[27] J.M. Gurd, Verbal fluency deficits in Parkinson's disease: individual differences in underlying cognitive mechanisms, Journal of Neurolinguistics 13(1) (2000) 47-55.

[28] S. Wyliea, W. van den Wildenbergb, K.Ridderinkhofb, T. Bashorec, V. Powella, C. Manninga, G. Wooten, The effect of speed-accuracy strategy on response interference control in Parkinson’s disease, Neuropsychologia, 47(0) (2009) 1844–1853.

[29] C. Strouwen, E. Molenaar, S.H.J. Keus, L. Munks, E. Heremans, W. Vandenberghe, B.R. Bloem, A. Nieuwboer, Are factors related to dual-task performance in people with Parkinson's disease dependent on the type of dual task?, Parkinsonism & Related Disorders 23 (2016) 23-30.

[30] A.F. Barbosa, C.D. Souza, J.N.N. Chen, D.V. Francato, F.A. Caromano, H.F. Chien, E.R. Barbosa, J.M.D. Greve, M.C. Voos, The competition with a concurrent cognitive task affects posturographic measures in patients with Parkinson disease, Arquivos De Neuro-Psiquiatria 73(11) (2015) 906-912.

[31] R. Marchese, M. Bove, G. Abbruzzese, Effect of cognitive and motor tasks on postural stability in Parkinson's disease: A posturographic study, Movement Disorders 18(6) (2003) 652-658.

[32] T.N. Tombaugh, Trail Making Test A and B: Normative data stratified by age and education, Archives of Clinical Neuropsychology 19(2) (2004) 203-214.

[33] B. Zarino, M. Crespi, M. Launi, A. Casarotti, A new standardization of semantic verbal fluency test, Neurological Sciences 35(9) (2014) 1405-1411.

4. CRITICAL ANALYSIS

This study aimed to describe the performance of patients with PD, compared to a control group, on an executive function upper limb task (Trail Making Test) and verbal fluency tasks (phonemic/semantic and oral diadochokinesia) and to investigate possible relationships between these measures (cognitive-motor interactions). Patients with PD showed more difficulty than controls in executive function, semantic and phonemic verbal fluency and oral diadochokinesia. Parts A and B of the Trail Making Test correlated to phonemic verbal fluency and to oral diadochokinesia. In our literature review, we did not find any other study that evaluated upper limbs and speech production tasks in the same protocol. The combination of these assessments adds to the understanding of the deficits generated by PD, especially the cognitive-motor interaction paradigm.

Possible cognitive-motor interactions must be considered in the assessment of patients with PD not to overestimate the cognitive or motor impairments. In our review study (Barbosa et al., 2016), the importance of sensory and cognitive systems in producing the motor response necessary to maintain dynamic balance and gait was emphasized. Patients with PD show gait instability related to executive dysfunction, and impaired motor planning (Levy et al., 2002; Marchese et al., 2003; Hanna-Pladdy, 2007; Stegemoller et al., 2014; Jacobs et al., 2014). Deficits become greater when there is a cognitive task to be performed concomitantly, because it competes for central resources. Opposite, dual-tasks can be improved when the cognitive components work as clue for motor performance (e.g. auditory cues facilitate gait cadence) (Stegemoller et al., 2014).

In a study carried out by our group (Barbosa et al., 2015), we explored cognitive-motor interactions in static balance of patients with PD. Participants were tested when deprived of visual information and when asked to perform a verbal fluency task. We observed that, compared to the matched age- and schooling-control group, patients with PD presented greater area and oscillation speed in the static posturography, mainly during the verbal fluency task. We concluded that the central processing speed and the motor planning capacity can be sensitized in the presence of a concomitant cognitive task that competes for central resources (Barbosa et al., 2015).

The cognitive-motor interaction was discussed by Bloem et al. (2006), in a literature review. The authors argued that elderly patients, especially the ones with PD, have difficulty maintaining the focus on the motor task when a cognitive task is added. Therefore, they have difficulty performing the motor task and show instability and falls. The decrease in the central processing capacity may be responsible for this phenomenon, since the death of dopaminergic neurons limits the capacity of processing afferent stimuli and planning appropriate motor responses. This theory, known as the bottleneck theory (Pashler, 1994) is supported in the review of Bloem et al. (2006) and the authors conclude that balance is even more sensitized when the cognitive task presented is unexpected. In the present study, considering the cognitive and motor components of the phonemic verbal fluency, it is probable that the motor component (speaking) is disturbing the phonemic memory processing (finding words with F).

Wickens' multiple resource theory expands and complements this theory, arguing that the performance is affected when the same neural networks are involved in both tasks of a dual-task (Voos et al., 2015; Barbosa et al., 2015; Strouwen et al., 2016). The frontal lobe, which is important in executive functions performance, is frequently activated in motor and cognitive tasks (Barbosa et al., 2015). When performing the part B of Trail Making Test, central processing is necessary for drawing the trail correctly and in the right order, alternating between numbers and letters. The cognitive overload in PD is due to the death of dopaminergic neurons in the basal ganglia. This neuronal loss leads to the difficulty in automatic movements and increases the need for cognitive supervision in tasks that could previously be performed with less cortical participation (Marchese et al., 2003).

Another theory highlights the involvement of non-dopaminergic pathways in PD, especially regarding non-motor symptoms. In PD patients diagnosed with dementia, cortical cholinergic denervation is frequently associated with frontal deficiency (Bohnen et al., 2003; Bohnen et al., 2015). The initial losses caused by the hypofunction of the dopaminergic pathways results in compensation by the cortical cholinergic neurons to prevent functional losses. As PD progresses, these pathways are also affected. The deleterious effect generated by the decreased activation of both the frontostriatal and the cholinergic systems is responsible for the increase in cognitive deficits and dementia (Biundo et al., 2014).

In the present study, we evaluated manual dexterity and executive function by the Trail Making Test and speech coordination and cognitive inhibition/ planning by verbal fluency tests (phonemic/ semantic and diadochokinesis). Patients with PD showed lower scores on all tests than controls. We found strong correlations between part A of Trail Making Test and oral diadochokinesia (p= -0.838), part B of Trail Making Test and phonemic verbal fluency (p= -0.874) and oral diadochokinesia (p= -0.824). Moderate correlations were also found between part A of Trail Making Test and phonemic verbal fluency (p= -0.712), between delta of Trail Making Test and phonemic verbal fluency (p= -0.740) and oral diadochokinesia (p= -0.689) and between oral diadochokinesia and phonemic verbal fluency (p= 0.684). We considered that these correlations reflect that cognitive-motor interactions are present in the Trail Making Test (even in part A), phonemic verbal fluency and oral diadochokinesis. The semantic verbal fluency (saying as many animals as possible in 60 seconds) seems to involve less cognitive demand, and consequently less cognitive-motor interaction than the phonemic verbal fluency (saying words with letter F).

The performance of patients with PD was better in semantic verbal fluency and we did not find correlations between this test and the Trail Making Test or the diadochocinesia tests due to the late involvement of non-dopaminergic pathways. The semantic verbal fluency test does not depend on frontal activation, but on other cerebral areas, such as the temporal lobe (Ellfolk et al., 2014), which is activated in patients in the moderate stage, as a compensatory activity. Therefore, it is possible that this test is a marker of the evolution for dementia, and that the deterioration in its performance may be related to the impairment of cortical cholinergic pathways (Bohnen et al., 2003; Bohnen et al., 2015).

4.1 IMPLICATIONS FOR REHABILITATION AND CLINICAL PRACTICE

Therapists must have in mind that all daily life activities, even speaking and writing, rely both on cognitive and motor systems. Cognitive-motor competition is frequent in patients with PD and this must be considered in the interpretation of clinical tests. Verbal fluency and paper and pencils tasks are not exclusively cognitive: they do not involve only executive function or speech. In PD, they may be disrupted by motor or cognitive-motor impairment. Motor planning impairment can influence speech production. Therapists must be careful not to overestimate cognitive deficits in patients with greater motor complications, e.g. diskinesias.

This study highlights the importance of evaluating situations of simultaneous motor and cognitive challenges of understanding the nature of each task. This information is important for the accurate evaluation of impairments and potentialities. If the therapist wants to assess any activity of daily living in patients with PD, options of lower and higher cognitive and motor demands must be explored. The therapist may choose to favor the motor task, and direct the cognitive demand as a cue for the task (e.g. a visual cue that shows feet position during the gait). The correct progression of therapeutic programs is possible with the understanding of the cognitive-motor interactions of specific tasks (Bloem et al., 2006; Petzinger et al., 2013). Patients with PD have difficulty walking and talking at the same time. The verbal fluency test is commonly used as a cognitive task in dual-task assessment during gait. However, it was not considered that besides the cognitive demand exerted by the verbal task, the motor system may also be overloaded, especially in more severe cases.

This study also highlights the importance of multidisciplinary intervention in PD rehabilitation. The cognitive-motor competition occurs in most tasks evaluated by health professionals. Interventions should consider the findings of the present study for therapeutic planning and clinical reasoning and decision making.

5. CONCLUSION

Patients with PD showed longer times than age- and education-matched controls in parts A and B and delta of the Trail Making Test, which evaluates executive function and hand dexterity. Patients with PD said less words in the phonemic and semantic verbal fluency tests and non-words in the diadochokinesis verbal fluency test.

There was a strong correlation between the phonemic verbal fluency test and the part B of Trail Making Test and between the oral diadochokinesia test and both parts of the Trail Making Test. The correlation between the part B of Trail Making Test, which is an executive function measure and reflects the cognitive-motor integration ability, and the verbal fluency tests, evidences the importance of motor control for speech tasks. Speech tasks not only provide cognitive overload, but also motor overload in patients with PD. This knowledge is important in clinical practice, in which therapists must detect the nature of the disability and the task to use this information properly in rehabilitation programs.

6. REFERENCES

Barbosa AF, Souza C de O, Chen J, Francato DV, Caromano FA, Chien HF, Barbosa ER, Greve JM, Voos MC. The competition with a concurrent cognitive task affects posturographic measures in patients with Parkinson disease. Arq Neuropsiquiatr. 2015;73(11):906-12.

Barbosa AF, Chen J, Freitag F, Valente D, Souza CO, Voos MC, Chien HF. Gait, posture and cognition in Parkinson's disease. Dement Neuropsychol. 2016;10(4):280-286.

Barbosa MT, Caramelli P, Maia DP, Cunningham MC, Guerra HL, Lima-Costa MF, Cardoso F. Parkinsonism and Parkinson's disease in the elderly: a community-based survey in Brazil (the Bambuí study). Mov Disord. 2006;21(6):800-8.

Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, et al. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov. Disord. 2009;24:1641–49.

Biundo R, Weis L, Facchini S, Formento-Dojot P, Vallelunga A, Pilleri M, Antonini A. Cognitive profiling of Parkinson disease patients with mild cognitive impairment and dementia. Parkinsonism Relat Disord. 2014;20(4):394-9.

Bloem BR, Grimbergen YA, van Dijk JG, Munneke M. The "posture second" strategy: a review of wrong priorities in Parkinson's disease. J Neurol Sci. 2006;248(1):196-204.

Blum D, Torch S, Lambeng N, Nissou M, Benabid AL, Sadoul R, Verna JM. Molecular pathways involved in the neurotoxicity of 6-OHDA, dopamine and MPTP: contribution to the apoptotic theory in Parkinson's disease. Prog Neurobiol. 2001:65(2)135-72.

Bohnen NI, Albin RL, Müller ML, Petrou M, Kotagal V, Koeppe RA, Scott PJ, Frey KA. Frequency of cholinergic and caudate nucleus dopaminergic deficits across the predemented cognitive spectrum of Parkinson disease and evidence of interaction effects. JAMA Neurol. 2015;72(2):194-200.

Bohnen NI, Kaufer DI, Ivanco LS, Lopresti B, Koeppe RA, Davis JG, Mathis CA, Moore RY, DeKosky ST. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. Arch Neurol. 2003;60(12):1745–48.

Brauer SG, Morris ME. Can people with Parkinson's disease improve dual tasking when walking? Gait Posture. 2010;31(2):229-33.

Brienesse LA, Emerson MN. Effects of Resistance Training for people with Parkinson’s disease: a systematic review. JAMA. 2013;14(4):236-41

Carvalho JAM, Rodríguez-Wong LL. A transição da estrutura etária da população brasileira na primeira metade do século XXI. Cadernos de Saúde Pública. 2008;24(3):597-605.

Cruise KE, Bucks RS, Loftus AM, Newton RU, Pegoraro R, Thomas MG. Exercise and Parkinson’s: Benefits for cognition and quality of life. J Ambulation. 2011;123(1):13-19.

Ellfolk U, Joutsa J, Rinne JO, Parkkola R, Jokinen P, Karrasch M. Striatal volume is related to phonemic verbal fluency but not to semantic or alternating verbal fluency in early Parkinson's disease. J Neural Transm. 2014:121(1):33-40.

Gurd JM. Verbal fluency deficits in Parkinson's disease: individual differences in underlying cognitive mechanisms. J Neurolinguist. 2000:13(1):47-55.

Hanna-Pladdy B. Dysexecutive Syndromes in Neurologic Disease. Journal of Neurologic Physical Therapy. 2007;31:119-27.

Jacobs JV, Nutt JG, Carlson-Kuhta P, Allen R, Horak FB. Dual tasking during postural stepping responses increases falls but not freezing in people with Parkinson's disease. Parkinsonism Relat Disord. 2014;20:779-81.

Jankovic J. Parkinson´s Disease: Clinical Features and Diagnosis. Journal of Neurology, Neurosurgery & Psychiatry. 2008;79:368-76.

Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: Progression to dementia. Mov. Disord. 2006;21:1343–1349.

Klein JC, Eggers C, Kalbe E, Weinsenbach S, Hohmann C, Vollmar S, Baudrexel S, Diederich NJ, Heiss WD, Hilker R. Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo. Neurology. 2010;74(11):885–892.

Lawson RA, Yarnall AJ, Duncan GW, Khoo TK, Breen DP, Barker RA, Collerton D, Taylor JP, Burn DJ. Quality of life and mild cognitive impairment in early Parkinson's disease: does subtype matter? J Parkinsons Dis. 2014;4(3):331-6.

Levy G, Jacobs DM, Tang MX, Côté LJ, Louis ED, Alfaro B, Mejia H, Stern Y, Marder K. Memory and executive function impairment predict dementia in Parkinson's disease. Mov Disord 2002;17:1221–1226.

Litvan I, Aarsland D, Adler CH, Goldman JG, Kulisevsky J, Mollenhauer B, et al. MDS Task Force on Mild Cognitive Impairment in Parkinson's Disease: Critical Review of PD-MCI. Mov Disord. 2011;26:1814-24.

Marchese R, Bove M, Abbruzzese G. Effect of cognitive and motor tasks on postural stability in Parkinson's disease: A posturographic study. Mov Disord. 2003;18(6):652-8.

McDowd J, Hoffman L, Rozek E, Lyons KE, Pahwa R, Burns J, Kemper S. Understanding Verbal Fluency in Healthy Aging, Alzheimer's Disease, and Parkinson's Disease. Neuropsychology. 2011;25(2):210-225.

Mills KA, Mari Z, Pontone GM, Pantelyat A, Zhang A, Yoritomo N, Powers E, Brandt J, Dawson TM, Rosenthal LS. Cognitive impairment in Parkinson's disease: Association between patient-reported and clinically measured outcomes. Parkinsonism Relat Disord. 2016;33:107-114.

Owen AM. Cognitive dysfunction in Parkinson disease: The role of frontostriatal circuitry. Neuroscientist. 2004;10:525-37.

Padovani M, Gielow I, Behlau M. Phonarticulatory diadochokinesis in young and elderly individuals. Arq Neuropsiquiatr. 2009;67(1):58-61.

Parkinson J. An essay on the shaking palsy. (1817). The journal of neuropsychiatry and clinical neurosciences. 2002;14(2):223-36.

Pashler H. Dual-task interference in simple tasks: data and theory. Psychology Bulletin. 1994;116(2):220-44.

Petzinger GM, Fisher BE, McEwen S, Beeler JA, Walsh JP, Jakowec MW. Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. Lancet Neurol. 2013;12(7):716-26.

Shapiro KA, Mottaghy FM, Schiller NO, Poeppel TD, Fluss MO, Muller HW, Caramazza A, Krause BJ. Dissociating neural correlates for nouns and verbs. Neuroimage. 2005;24(4):1058-1067.

Souza CO, Voos MC, Francato DV, Chien HF, Barbosa ER. Influence of Educational Status on Executive Function and Functional Balance in Individuals with Parkinson Disease. Cogn Behav Neurol. 2013;26(1):6-13.

Stegemöller EL, Wilson JP, Hazamy A, Shelley MC, Okun MS, Altmann LJ, Hass CJ. Associations between cognitive and gait performance during single- and dual-task walking in people with Parkinson Disease. Phys Ther. 2014;94:757-766.

Strouwen C, Molenaar E, Keus SHJ, Munks L, Heremans E, Vandenberghe W, Bloem BR, Nieuwboer A. Are factors related to dual-task performance in people with Parkinson's disease dependent on the type of dual task? Parkinsonism Relat Disord. 2016;23:23-30.

Tombaugh TN. Trail Making Test A and B: Normative data stratified by age and education. Arch Clin Neuropsychol. 2004;19(2):203-14.

Voos MC, Piemonte MEP, Castelli LZ, Machado MSA, Teixeira PPS, Caromano FA. Association between educacional status and dual-task performance in Young adults. Percept Mot Skills. 2015;120(2):417-437.

Wyliea S, van den Wildenbergb W, Ridderinkhofb K, Bashorec T, Powella V, Manninga C, Wooten G. The effect of speed-accuracy strategy on response interference control in Parkinson's disease. Neuropsychologia. 2009;47:1844–53.

Zarino B, M. Crespi, M. Launi, A. Casarotti. A new standardization of semantic verbal fluency test. Neurol Sci. 2014:35(9):1405-11.

7. ANEXOS

ANEXO 1 – Artigo publicado na revista Arquivos de Neuro-Psiquiatria.

The competition with a concurrent cognitive task disrupted posturographic measures in Parkinson disease

A competição com uma tarefa cognitiva afeta medidas posturográficas de pacientes com doença de Parkinson

Alessandra Ferreira Barbosa[1,2,3], Carolina de Oliveira Souza[2,3], Janini Chen[2,3], Débora Valente Francato[2,3], Fátima Aparecida Caromano[1], Hsin Fen Chien[2,3], Egberto Reis Barbosa[3], Júlia Maria D´Andrea Greve[4], Mariana Callil Voos[1,2]

1. Department of Physical Therapy, Occupational Therapy and Speech Therapy of University of São Paulo, School of Medicine. Brazil.
2. REMOVE. Rehabilitation in Movement Disorders. São Paulo. Brazil.
3. Movement Disorder Clinic. Department of Neurology of University of São Paulo, School of Medicine. Brazil.
4. Department of Orthopedics of University of São Paulo, School of Medicine. Brazil.

Correspondence: Alessandra Ferreira Barbosa, PT, MSc student, alefbar@gmail.com, Rua Capote Valente, 395, apartamento 12, CEP: 05409-001, São Paulo, Brasil. Telephone: +5511995520002.

Additional information: This study was conducted at Faculdade de Medicina da Universidade de São Paulo, Brasil. No funding to declare.

ABSTRACT

Objectives: To estimate the impact of a sensory and a cognitive task on postural balance, in Parkinson disease patients (Hoehn & Yahr 2-3) and to investigate possible relationships between posturography and functional balance clinical scales. **Design:** Parkinson disease patients (n=40) and healthy controls (n=27) were evaluated with fluency tests, Berg Balance scale, Mini Best test and static posturography on the conditions eyes open, eyes closed and dual-task (simultaneous balance and fluency tasks). **Results:** Posturographic data showed that Parkinson disease patients performed worse than controls in all evaluations. In general, balance on dual-task was significantly poorer than balance with eyes closed. Posturographic data were not correlated to the clinical balance scales. **Conclusion:** In clinical practice Parkinson disease patients are commonly assessed with eyes closed, to sensitize balance. Our study showed that adding a cognitive task is even more effective. Static posturographic data cannot be overgeneralized to infer functional balance impairments.

Key words: Parkinson disease, postural balance, cognition, aging

RESUMO

Objetivos: Estimar o impacto de uma tarefa sensorial e uma tarefa cognitiva no equilíbrio postural, em pacientes com doença de Parkinson e investigar possíveis relações entre dados posturográficos e escalas clínicas de equilíbrio. **Métodos:** Pacientes (n=40) e controles (n=27) foram avaliados com testes de fluência verbal, escala de equilíbrio de Berg (BBS), Mini Best Test (MBT) e posturografia estática nas condições olhos abertos, olhos fechados e tarefa-dupla (equilíbrio e fluência, simultaneamente). **Resultados:** Dados posturográficos mostraram que pacientes com Parkinson apresentaram pior desempenho que controles em todas as avaliações. O equilíbrio na dupla-tarefa foi significativamente pior que na privação visual. Os dados posturográficos não se correlacionaram com BBS ou MBT. **Conclusão:** Pacientes com Parkinson são comumente avaliados com olhos fechados para sensibilizar o equilíbrio. Nosso estudo mostra que a adição de uma tarefa cognitiva é mais efetiva. A posturografia estática não pode ser generalizada para inferir alterações de equilíbrio nesses pacientes.

Palavras-chave: Doença de Parkinson, equilíbrio postural, cognição, envelhecimento

INTRODUCTION

Parkinson disease (PD) is a progressive degenerative disorder of the central nervous system, and affects 1.5 to 2.0% of the elder population (above 60 years of age)[1]. It is typically characterized by tremors, muscle rigidity, bradykinesia, diskinesia and loss of adaptive responses as muscle strength and aerobic capacity[1-2]. One of the most important disabilities that appear on the course of the disease is the postural instability, which is also one of the main challenges in PD rehabilitation[3,4]. Recent studies have shown that non-motor disorders are also present in these patients[1,5], e.g. humor, sleep, executive function, social behavior[6].

The mechanisms associated with postural instability are still not fully understood. Studies suggest the dysfunctioning of the pedunculopontine nucleus, leads to the loss of anticipatory and compensatory postural responses automation, and disrupts sensory-motor integration (processing of visual, proprioceptive and vestibular information and motor response selection)[3,7-9]. Postural control deficits enhance trunk and knees flexion and increases the need for attentional control over posture[4]. Postural instability is a major cause of disability in these patients, exposing them to increased fall risk, insecurity and restrictions on movement and daily life activities[10].

Similarly, cognitive deficits, specifically in executive functions, can significantly affect functional independence and compromise security. Executive function is a broad concept that includes the ability to monitor and process internal and external information, attend to multiple tasks concurrently, set and achieves goals, solve problems, and regulate environmental demands. As PD progresses, the executive function and postural control deteriorate and the degree of cognitive-motor dependency increases[11,12].

Diverse tools as Timed up and Go test (TUG), Berg Balance Scale (BBS), 6-minutes walking test, dynamic gait index and, more recently, MiniBEST test (MBT)[11] evaluate postural control in PD patients. Beyond these clinical assessments, the gold-standard evaluation of postural control is computerized posturography. This kinetic evaluation measures the center of pressure oscillation in order to assess the efficiency of postural control adjustments[13].

Although many authors have used this tool to evaluate the postural instability of patients with PD, the results are still inconclusive[14]. Furthermore, variations in the adopted methods and variables make it difficult to compare studies. Ickenstein et al.[7] studied a methodology that could differentiate patients with PD from healthy controls. The chosen task was an adapted version of Romberg's test in two conditions, eyes open and eyes closed, evaluated by variables drawn from the oscillation trajectory. This method was able to differentiate the two groups, especially in visual deprivation.

Johnson et al.[14] aimed to differentiate PD patients with a fall history from more stable patients and healthy controls using a combination of clinical tests and static posturography. Area oscillation measurement differentiated PD patients and healthy controls with a fall history. The study also found positive correlations between BBS, TUG and oscillation area. The reaction time was an important variable to distinguish the three groups; this variable was dependent on cognitive processing. Cognitive tasks, when associated with motor tasks, cause major disturbance in PD patients. Such negative cognitive-motor interaction is documented in balance and gait in PD patients[15-18].

Many studies have found the effect of sensory disturbance in static balance, but few evaluated the cognitive task addition effect. Marchese et al.[3] evaluated the static posturography in patients with PD and age matched controls in static posture conditions, associated with a simple motor task, and a cognitive task, with and without visual deprivation. They found greater disturbance on balance in the cognitive task and no effect regardless of the visual condition.

Despite the different methodologies employed, the latest results point to the worsening of postural control in conditions of sensory disturbance, and in association with cognitive tasks, poorly described for static postural control. However, studies fail to clarify whether the static posturography would be an effective tool for clinical assessment and whether it could be related to clinical balance assessment.

The aim of this study was to investigate whether the association of a cognitive task would affect postural control in patients with PD in the same way that visual deprivation. The secondary objective was to investigate a possible relationship between the static posturography data and clinical balance scales.

METHODS

Subjects

This study was approved by the committee on research ethics at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo in accordance with the Declaration of the World Medical Association and all participants read and signed a written informed consent approved by this committee. Fifty-nine healthy elderlies from a senior center of the University of São Paulo Clinics Hospital were invited to participate in the control group. Thirty-five volunteered and twenty-seven met the inclusion criteria, gave informed consent and underwent cognitive-motor assessment protocol.

For both control and experimental groups, only people aged between 60 and 79 years, with 5 or more years of formal education and with a minimal Mini-mental score of 24[19], according to the cut-off determined by the Brazilian version of the test were included. Subjects with acute or terminal illnesses, myocardial infarction in the last six months, moderate or severe chronic obstructive pulmonary disease, uncontrolled hypertension, uncontrolled metabolic disease, acute orthopedic injuries, and other neurological and/or muscular disease were excluded from the study.

Seventy-eight outpatients with idiopathic PD, from the movement disorders clinic of the University of São Paulo Clinics Hospital were invited to participate in the experimental group. Fifty-two volunteered and forty met our inclusion criteria and gave informed consent. Additional inclusion criteria for PD patients comprehended having received the diagnosis of PD according to the clinical criteria of the United Kingdom Parkinson´s Disease Society Brain Bank[20]; Hoehn & Yahr[21] (H&Y) score between 2 and 3; being on antiparkinsonian drug treatment at a stable and optimized daily dosage during the last 4 weeks prior to study entry.

Procedures

Participants were assessed individually, on one session. After receiving detailed explanation about the study, they signed the informed consent. Both groups were assessed with the Mini-mental state examination, fluency tests (animals: saying animals names and phonemic: saying words beginning with letter F), BBS, MBT and static posturography. All the patients with PD were on their best “on” state.

Cognitive assessment

All participants underwent cognitive assessment comfortably seated on a chair placed in front of a table. The mini-mental test screened for severe cognitive impairment and only subjects scoring above 24 points were included[19]. In the fluency test, subjects were instructed to say as many as animals as they could remember in one minute, without repetition or gender changing. Each word was scored with one point and repeated words were not scored, this test has been found to be a predictor of latter development of dementia[22].

Motor assessment

The BBS is a widely-used measure of balance and has been validated for the PD patients. It consists of a 14-item scale, scored from zero to four (best), assessing abilities involving sitting, standing and positional changes[23]. The MBT is a more recent tool developed to assess balance. It involves four domains: anticipatory, sensory, gait and reactive and totalizes 14 items, scored from 0 to 2 (best performance). It has a high correlation with BBS, but the combination BBS-MBT reduces the ceiling effect of higher scored patients[24].

Cognitive-motor assessment

Participants stood barefoot on a 0.5 X 0.5 m platform (AMTI Accusway Plus; Advanced Mechanical Technology, Inc., Watertown, Massachusetts, USA) with their arms alongside the body and their feet 5 cm apart. Feet positions were marked and kept the same in all trials.The frequency of acquisition was set up at 100 Hz.

Data were collected in three trials of 60 seconds, under three conditions: (i) keeping balance with eyes open (EO); (ii) keeping balance with eyes closed (EC); (iii) dual-task (DT): keeping balance with eyes open and performing three fluency tasks: saying as many words as possible starting with letter F (trial 1), words starting with letter P (trial 2) and naming fruits (trial 3). Each trial lasted for one minute.

Descriptive measures of the center of pressure (COP) displacement oscillation were collected by posturography: the mean velocity of the COP oscillation (Vavg), the elliptical area covering 95% of the COP projection points (area) and the standard deviations of the COP oscillation on both axes, mediolateral (SD-ML) and anteroposterior (SD-AP).

Rocchi et al.[13] analysed fourteen variables related to the COP and concluded that standard deviation and mean velocity, provided insights about the postural control mechanisms and described changes in postural strategies. The area were chosen for being widely used in other posturography studies.

Statistical analysis

Data with normal distribution were expressed as means±standard deviations (SD). The level of significance was set at alfa<0.05. Student Tests t were used to compare the groups in terms of age, height, weight and number of years of formal education. Qui-square tests investigated sex distribution differences.

Analyses of Variance (ANOVAs) were performed to compare both groups and the three evaluation conditions on the posturography, as dependent variables**.** When a significantly interaction was found, Tukey post hoc tests were performed to complement the analysis. Additionally, Spearman correlation tests compared the performance on the balance scales with the results of the posturographic evaluation.

RESULTS

Clinical Data

Table 1 shows demographic data and test scores for patients with PD and healthy controls. No significant differences were found in age, education, gender, height, weight and cognitive screening (Table 1).

Table 2: Demographic data for patients with Parkinson Disease and healthy controls

Groups	PD	Controls	P
Age (years)	67.17±4.3	68.37±3.7	0.115
Education (years)	9.77±4.87	11.15±4.53	0.121
Gender (F/M)	16/24	17/10	0.349
Mean height	1.65±0.09	1.61±0.08	0.603
Mean weight	70.5±12.96	69.8±7.26	0.391
Mini-mental score	27.7±2.09	28.07±1.07	0.340

*p < 0,05. PD: Parkinson disease;

Cognitive assessment

The fluency test naming animals found significant difference between groups (p=0.001). PD patients said significantly fewer words than the control group on both tasks.

Motor assessment

Both clinical assessment tests, BBS and MBT, were sensitive in discriminating the PD group from control group ($p=0.007$ and $p<0.001$, respectively).

Cognitive-motor assessment

Mean velocity: ANOVA showed that the mean velocity of the COP oscillation (Vavg) showed significant differences for groups ($p=0.020$) and conditions ($p<0.001$), but no interaction groups vs. conditions ($p=0.894$) (Figure 1). For both groups, the velocity of body sway and the data confidence interval (data variability) gradually increased from eyes open to eyes closed conditions and from eyes closed to dual-task.

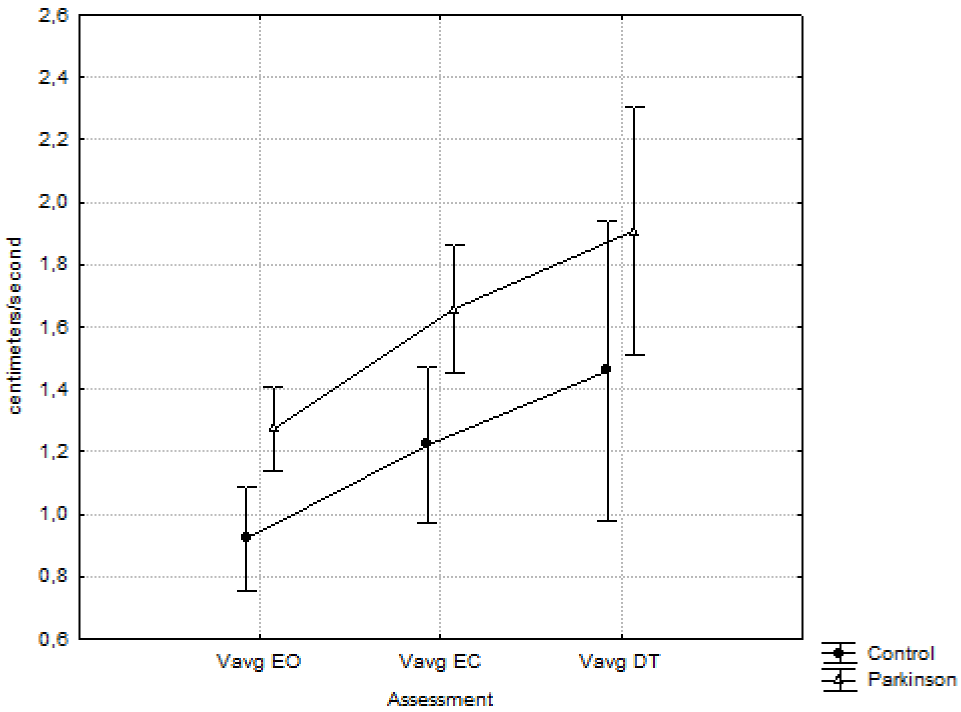


Figure 1: Performance of the groups on the three conditions (EO: eyes open, EC: eyes closed, DT: dual-task) for the variable average velocity of oscillation (Vavg).

Elliptical area: The elliptical area covering 95% of the COP projection points and the standard deviation of the COP oscillation on mediolateral axis (SD-ML) showed similar variations on the three conditions. Significant differences were observed between groups (p=0.010) and conditions (p<0.001), but no interaction groups vs. conditions (p=0.771) (Figure 2). Both groups had greater postural sway on the dual-task condition, comparing the condition eyes open to the condition eyes closed. The addition of the cognitive task had more impact on postural control than the visual deprivation for both groups on both variables. A higher variability in performance (a higher confidence interval) was observed on dual-task conditions.

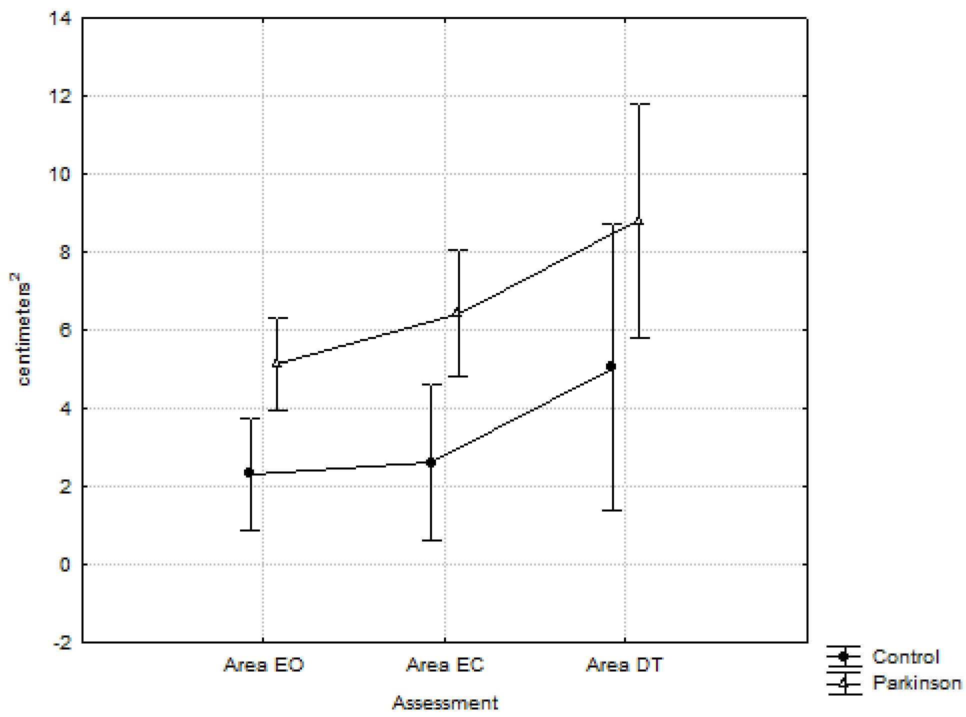


Figure 2: Performance of the groups in the three conditions for the variable elliptical Area covering 95% of the trajectory points.

Standard deviation of the COP oscillation on mediolateral axis: The standard deviation of the COP oscillation on mediolateral axis (SD-ML) also showed a significant difference between groups (p=0.001) and conditions (p<0.001), but no interaction groups vs. conditions (p=0.834) (Figure 3). Both groups had greater postural sway on the dual-task condition, comparing the condition eyes open to the condition eyes closed. The addition of the cognitive task had more impact on postural control than the visual deprivation for both groups on both variables. A higher variability in performance (a higher confidence interval) was observed on dual-task conditions.

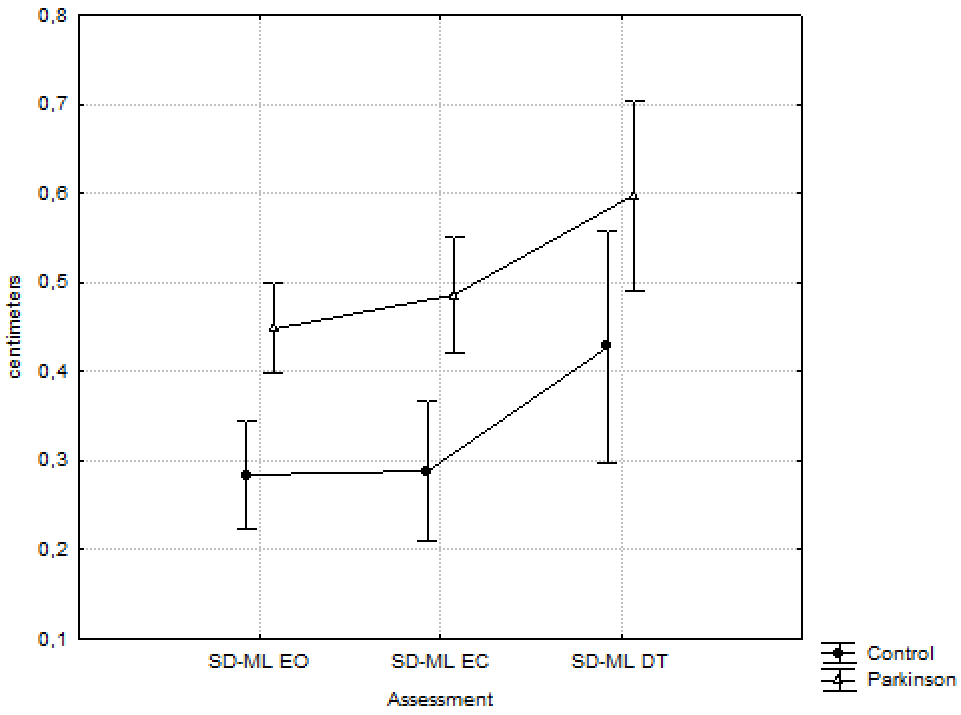


Figure 3: Performance of the groups in the three conditions for the variable mediolateral standard deviation (SD-ML).

Standard deviation of the COP oscillation on anteroposterior axis: The standard deviation of the COP oscillation on anteroposterior axis (AP-SD) showed a significant difference between groups (p=0.007), conditions (p<0.001), and also a significant interaction groups vs. conditions (p=0.027). PD patients showed a higher

SD-AP during the whole assessment, while controls gradually increased their SD-AP on the conditions eyes closed and dual-task (p=0.0005) (Figure 4).

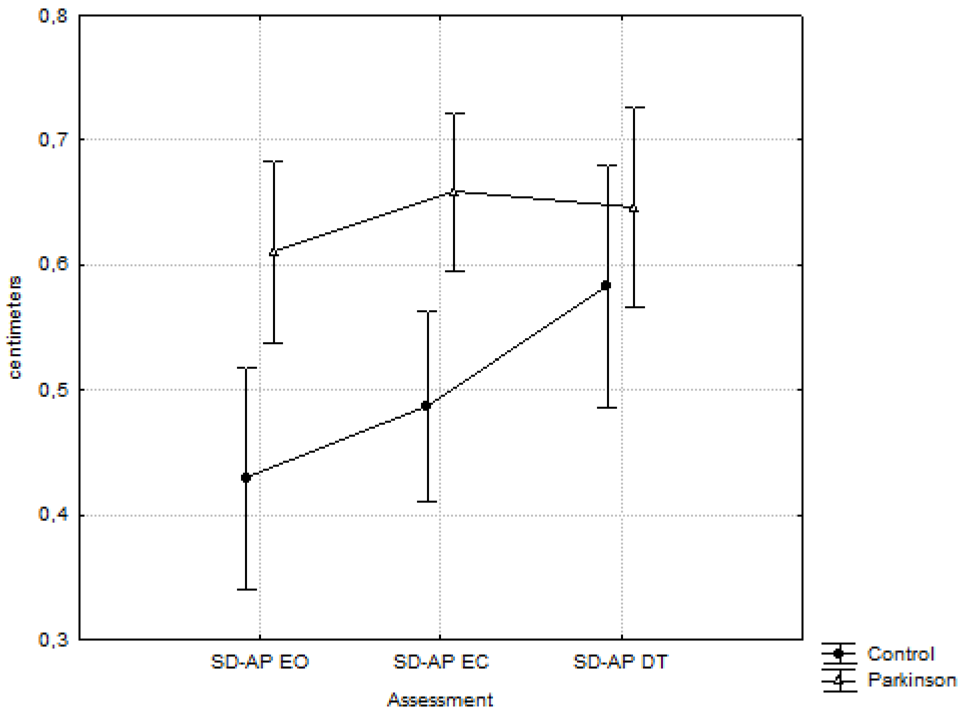


Figure 4: Performance of the groups in the three conditions for the variable anteroposterior standard deviation (SD-AP).

Relations between the clinical tests and posturography

Spearman correlation tests were performed with the the PD group data. Possible relationships between the posturographic variables, the BBS and the MBT were investigated. The results are displayed in Table 2.

Table 2: Relationships between posturographic and clinical data for patients with Parkinson Disease

		Control		PD	
		MBT	BBS	MBT	BBS
EO	SD-ML	-0.142975	0.074201	-0.223594	-0.338070
	SD-AP	-0.074758	0.232312	0.207128	0.114849
	Vavg	0.003115	-0.241674	-0.078893	-0.005660
	Area	-0.062299	0.210121	-0.039258	-0.171488
EC	SD-ML	-0.388180	-0.229920	-0.121729	-0.242894
	SD-AP	-0.087401	0.101277	0.305703	0.168194
	Vavg	-0.084415	-0.459076	0.112315	0.092724
	Area	-0.320527	-0.130719	-0.004142	-0.146585
DT	SD-ML	-0.297034	-0.169657	-0.098475	-0.160640
	SD-AP	-0.042363	0.236473	0.194512	0.065561
	Vavg	-0.103899	-0.273962	0.032009	0.101497
	Area	-0.238604	0.027392	-0.002259	-0.107345

MBT: MiniBEST test; BBS: Berg balance scale, EO: eyes open; EC: eyes closed; DT: dual-task condition; SD-ML: mediolateral standard deviation; SD-AP: anteroposterior standard deviation; Vavg: average velocity off oscillation; Area: elliptical area covering 95% off trajectory oscillation.

DISCUSSION

The present study investigated whether the association of a cognitive task would affect postural control in patients with PD in the same way that visual deprivation. It was found distinct modifications of posturographic data on the conditions eyes open, eyes closed and dual-task. Some differences between the experimental PD group and the control group were also observed.

It is well known that physiological aging impairs the processing of visual, vestibular and somatosensory information, which may also affect the postural control[25].

Healthy older people tend to rely more on visual information than on somatosensory information and, in cases of sensory conflict, can present difficulty using vestibular information for postural control[25]. PD patients present a similar behavior as presented by Lee et al.[8], who showed that PD patients depend on vestibular information. The authors hypothesized, in agreement with Yen et al.[4], that balance impairments were associated with deficits in sensory processing and/or in the central integration of sensory information.

Beyond this natural aging process, other factors may contribute to balance disruption facing sensory disturbance, in this population. Loss of automation in performing postural changes can increase the dependence on visual information[26]. Studies of Ickenstein et al[7]. and Rossi et al[27]. pointed to the increase of visual dependence, as a compensation mechanism, and explained that the overload of the visual system can affect postural control, as detected by posturography.

Changes on postural control due to sensory disturbance have been well described, such as changes on gait parameters in dual-task conditions, for both healthy elderly and PD patients[16,17]. However, our results add interesting data, because they showed that the competition with a concurrent cognitive activity disrupted posturographic measures distinctly.

For both groups, the elliptical area and the SD-ML did not change significantly on eyes closed condition, compared to eyes open condition, but they increased on dual-task, compared to eyes closed. For the dual-task condition Marchese et al.[3] had shown that elliptical area had been sensible to show the differences between conditions and groups, justified for the amount of compensatory stabilizing movements in both planes, needed by PD patients to maintain balance. However, Brown et al.[28] proved that despite

PD patients present deficit in the reorganization of oscillation area after visual deprivation, this condition tends to stabilize after a period of time, which probably occurred in our sample for the two variables.

The velocity of body sway increased with eyes closed, compared to the eyes open condition and on dual-task, compared to eyes closed. No other studies investigating the velocity of body sway with eyes open, closed and dual-taskwere found, but Rocchi et al.[18] reported a correlation between the velocity and the items related to tremor from the Unified Parkinson Disease Rating Scale. Therefore, it was expected that the PD group would show greater speed oscillation in all conditions, increasing according to the difficulty of the task, as well as the control group.

The groups showed distinct reactions on anteroposterior sway assessment. PD patients showed a high anteroposterior sway on all conditions, while controls showed gradual anteroposterior sway increase with eyes closed, compared to eyes open and on dual-task, compared to eyes closed. In the literature review it was not found results like these, but we hypothesized that this finding might be attributed to a ceiling effect. On the sample of the present study, the patients had a high variation in the oscillation, which refers to the level of stability. Therefore, PD patients were less able than the control group to adapt to all conditions. This variable may be useful distinguishing PD and control groups, but not to evaluate the effects of a disturbance in postural control for PD patients.

Our results corroborate with the ones from Marchese et al.[3] who noticed the worsening on postural sway area and path, variable that could be related to mean velocity, during a cognitive task. In their study they describe that the PD group and the control group were even more different when the PD group was divided considering the falls history and they pointed as possible causes for their findings the reduction of atentional capacity, a longer established balance deficit and the great resources competition for planning and production of the appropriate motor response.

Considering these results, it is possible to conclude that static posturography alterations on dual-task conditions can signal a major problem for the central processing and motor planning, thus subjecting individuals with Parkinson's to a high risk of falling.

It was also investigated possible relationships between static posturography data and clinical functional balance assessment. Such relationships are still poorly studied and must be carefully applied to clinical practice. Our study showed no correlation between the posturographic variables and the clinical balance scales (BBS and MBT).

The application of the two scales showed great power of differentiation between the two groups, with a significant worsening of the balance in the PD group. This was due to the fact that both scales evaluated more dynamic conditions, such as transferring and keeping a decreased base of balance. Lee et al.[8] found strong correlations between cognitive tasks and balance on more challenging situations, indicating that the integrity of executive functions is important for planning adjustments to maintain the posture. Future studies should investigate whether the training of static balance associated with cognitive demands could be effective decreasing postural sway on dual-task, similar to that observed on gait training.

CONCLUSION

In clinical evaluation of neurological patients, it is common to ask patients to close their eyes in order to sensitize postural control and highlight balance disorders.

Our results indicate that in cognitive dual-task conditions the change in postural control can be even greater than with visual deprivation and it is suspected that this interaction is greater in individuals with larger balance disorders, evidenced by the fall history.

Postural change in such cases should signal to the physicians and therapists greater need for attention and balance training activities with varying degrees of difficulty, including the maintenance of static posture. It was not possible to correlate the variables of posturography with the balance scales, widely used in the clinic. It is suggested that further studies are conducted, including posturography in dynamic conditions, to clarify this relationship.

REFERENCES

1. Brienesse L. A., Emerson M. N. Effects of Resistance Training for people with Parkinson's disease: a systematic review. *JAMA*. 2013;14:236-241.

2. Van der Kolk N., King L. Effects of exercise on mobility in people with Parkinson's disease. *Mov Disord*. 2013;28:1587-96.

3. Marchese R., Bove M., Abruzzese G. Effect of cognitive and motor tasks on postural stability in Parkinson's disease: A posturographic study. *Mov Disord*. 2003;18:652-658.

4. Yen C, Kwan L, Ming H. Effects of virtual realityaugmented balance training on sensory organization and attentional demand for postural control in people with Parkinson disease: A randomized controlled trial.*Phys Ther*.2011;91:862-874.

5. Cruise KE, Bucks RS, Loftus AM, et al. Exercise and Parkinson's: Benefits for cognition and quality of life. *Acta Neurol Scand*. 2011;123:13-19.

6. Reijnders J. S. M., Ehrt .U, Lousberg R., Aarsland D., Leentjens A. F. G., The association between motor subtypes and pshychopathology in Parkinson's disease. *Parkinsonism Relat Disord*. 2009;15:379-382.

7. Ickenstein GW, Ambach H, Klöditz A, et al. Static Posturography in aging and Parkinson's disease. *Front aging neurosci.* 2012;4:20. doi: 10.3389/fnagi.2012.00020.

8. Lee JM, Koh SB, Chae SW, et al. Postural instability and cognitive dysfunction in early Parkinson's disease. *Can J Neurol Sci.* 2012;39:473-482.

9. Stefani A, Lozano A, Peppe A, et al. Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. *Brain*. 2007;130:1596-1607.

10. Frenklach A, Luie S, Koop MM, Bronte-Stewart H. Excessive postural sway and the risk of falls at different stages of Parkinson's disease. *Mov Disord*. 2009;24:377-385.

11. Liu-Ambrose TY, Ashe MC, Graf P, et al. Increased risk of falling in older community-dwelling women with mild cognitive impairment. *Phys Ther*. 2008;88:1482–1491.

16. Souza C. O., Voos M.C., Francato D. V., Chien H. F., Barbosa E. R. Influence of educational status on executive function and functional balance in individuals with Parkinson disease. *Cogn Behav Neurol.* 2013;26:6-13.

13. Rocchi L, Chiari L, Cappello A, Horak FB. Identification of distinct characteristics of postural sway in Parkinson's disease: a feature selection procedure based on principal component analysis. *Neurosci Lett.* 2006;394:140-145.

14. Johnson L, James I, Rodrigues J, Stell R, Thickbroom G, Mastaglia F. Clinical and posturographic correlates of falling in Parkinson's disease. *Mov Disord.* 2013;28:1250-1256.

15. Voos MC, Pinheiro GB, Cicca LO, Lázaro A, Valle LER, Piemonte MEP. Os componentes motor e visual de uma tarefa-dupla devem ser associados ou isolados durante o treinamento? *Fisioterapia e Pesquisa*. 2008;15:33-39.

16. Van Iersel MB, Kessels RPC, Bloem BR, Verbeek ALM, Rikkert MGMO. Executive functions are associated with gait and balance in community-living elderly people. *J Gerontol A Biol Sci Med Sci*. 2008;63:1344-1349.

17. Stegemöller EL, Wilson JP, Hazamy A, et al. Associations between cognitive and gait performance during single- and dual-task walking in people with Parkinson Disease. *Phys Ther*. 2014;94:757-766.

18. Ebersbach G, Gunkel M. Posturography reflects clinical imbalance in Parkinson's disease. *Mov Disord.* 2011;26:241-246.

19. Brucki SMD, Nitrini R, Caramelli P, et al. Sugestões para o uso do mini-exame do estado mental no Brasil. *Arq Neuropsiquiatr*. 2003;61:777–781.

20. Metman LV, Myre B, Verney N, et al. Test-retest reliability of UPDRS- III, dyskinesia scales, and timed motor test in patients with advanced Parkinson's disease: an argument against multiple baseline assessments. *Mov Disord*. 2004;19:1079–1084.

21. Hoehn MM, Yahr MD. Parkinsonism-onset progression and mortality. *Neurology*. 1967;17:427-42.

22. Brucki SM, Rocha MS. Category fluency test: effects of age, gender and education on total scores, clustering and switching in Brazilian Portuguese-speaking subjects. *Braz J Med Biol Res.* 2004;37:1771-1777.

23. Qutubuddin AA, Pegg P, Cifu D, Brown R, McNamee S, Carne W. Validating the Berg Balance Scale for Individu- als with Parkinson's Disease: A Key to Rehabilitation Evaluation. *Arch Phys Med Rehabil*. 2005;86:789–792.

24. Godi M, Franchignoni F, Caligari M, Giordano A, Turcato AM, Nardone A. Comparison of Reliability, Validity and responsiveness of the Mini-BESTest and Berg Balance Scale in patients with Balance Disorders. *Phys Ther*. 2013;93:158-167.

25. **S**humway-Cook A, Woollacott MH. *Motor control: theory and practical applications.* 2nd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2001.

26. Azulay JP, Mesure S, Amblard B, Blin O, Sangla I, Pouget J. Visual control of locomotion in Parkinson's disease. *Brain.* 1999;122:111-20.

27. Rossi M, Soto A, Santos S, Sasar A, Labella T. A prospective study of alterations in balance among patients with Parkinson's Disease. *Eur Neurol.* 2009;61:171-176.

28. Brown LA, Cooper SA, Doan JB et al. Parkinsonian deficits in sensory integration for postural control: Temporal response to changes in visual input. *Parkinsonism Relat Disord.* 2006;12:376-381.

ANEXO 2 – Resumo apresentado na 6ª Reunião do Departamento Científico de Transtornos do Movimento da Academia Brasileira de Neurologia

INTERAÇÃO SENSÓRIO-COGNITIVO-MOTORA NO EQUILÍBRIO POSTURAL DE PACIENTES COM DOENÇA DE PARKINSON

Alessandra Ferreira Barbosa[1,2], Carolina de Oliveira Souza[1,2], Hsin Fen Chien[1,2], Janini Chen[1,2], Egberto Reis Barbosa[1], Mariana Callil Voos[2, 3].

1. Clínica de Distúrbios do Movimento, Departamento de Neurologia. Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Brasil.

2. ReMove – Reabilitação em Distúrbios do Movimento.

3.Departamento de Fonoaudiologia, Fisioterapia e Terapia Ocupacional. Faculdade de Medicina da Universidade de São Paulo, Brasil.

Introdução: A instabilidade postural é um grande desafio na reabilitação de pacientes com Doença de Parkinson. Ela se agrava com a evolução da doença, porém ainda não são compreendidos todos os mecanismos envolvidos em sua causa. Da mesma forma, os déficits cognitivos também se agravam com a evolução da doença o que pode acarretar um maior risco de queda principalmente em situações de associação da tarefa cognitiva com uma tarefa motora.

Objetivos: Comparar o impacto de uma tarefa sensorial e uma tarefa cognitiva no equilíbrio postural, em pacientes com doença de Parkinson e investigar possíveis relações entre dados posturográficos e escalas clínicas de equilíbrio.

Métodos: Foram avaliados 40 pacientes com doença de Parkinson (Hoehn & Yahr: 2-3) e 27 idosos saudáveis de idade pareada. Ambos os grupos foram avaliados com testes de fluência verbal, enquanto sentados, escala de equilíbrio de Berg (BBS), Mini Best Test

(MBT) e posturografia estática nas condições olhos abertos, olhos fechados e dupla-tarefa (equilíbrio e fluência, simultaneamente).

Resultados: Dados posturográficos mostraram que pacientes com Parkinson apresentaram pior desempenho que idosos saudáveis em todas as avaliações. Na velocidade média, área elíptica e desvio padrão mediolateral os grupos se comportaram de maneira similar, com piora gradativa na oscilação, sendo piores na condição de dupla tarefa. O equilíbrio na dupla-tarefa foi significativamente pior que na privação visual, nessas variáveis. A variável desvio-padrão anteroposterior mostra um comportamento diferente, sendo que desde a primeira condição, os pacientes já mostram uma grande dispersão no equilíbrio, que se manteve alta nas condições mais desafiantes, enquanto o grupo controle mantém o aumento gradativo. Os dados posturográficos não se correlacionaram com BBS ou MBT.

Conclusão: Muitos estudos avaliam o efeito da tarefa cognitiva no desempenho da marcha de pacientes com Parkinson, porém pouco se fala sobre esse efeito no equilíbrio estático. Pacientes com Parkinson são comumente avaliados com olhos fechados para sensibilizar o equilíbrio estático; nosso estudo mostra que a adição de uma tarefa cognitiva ainda é mais eficiente nessa perturbação. Além disso, a posturografia estática não se correlacionou com as escalas de equilíbrio, o que indica que é necessário muito cuidado para generalizar esses dados para inferir alterações de equilíbrio nesses pacientes.

ANEXO 3 – Artigo publicado na revista Dementia & Neuropsychologia

GAIT, POSTURE AND COGNITION IN PARKINSON'S DISEASE

MARCHA, POSTURA E COGNIÇÃO NA DOENÇA DE PARKINSON

Alessandra Ferreira Barbosa[1,3], Janini Chen[2,3], Fernanda Freitag[2], Debora Valente[2,3], Carolina de Oliveira Souza[2,3], Mariana Callil Voos[1,3], Hsin Fen Chien[2,3,4]

The first two authors equally contributed to this article.

1. Physical Therapy, Occupational Therapy and Speech Therapy Department, University of São Paulo School of Medicine, São Paulo, SP, Brazil.
2. Movement Disorders Clinic of Hospital das Clinicas of the Department of Neurology. University of São Paulo School of Medicine, São Paulo, SP, Brazil.
3. ReMove. Rehabilitation of Movement Disorders Research Group.
4. Institute of Orthopedics and Traumatology of Hospital das Clínicas of University of São Paulo School of Medicine, São Paulo, SP, Brazil.

Correspondence: Hsin Fen Chien. Rua Vergueiro, 1421 / cj 1506 – 04101-000. São Paulo SP – Brazil. E-mail: chien.hfen@hc.fm.usp.br

Disclosure: The authors report no conflicts of interest.

Reference: Barbosa AF, Chen J, Freitag F, Valente D, Souza CO, Voos MC, Chien HF. Gait, posture and cognition in Parkinson's disease. Dement Neuropsychol. 2016;10(4):280-286.

ABSTRACT. Gait disorders and postural instability are the leading causes of falls and disability in Parkinson's disease (PD). Cognition plays an important role in postural control and may interfere with gait and posture assessment and treatment. It is important to recognize gait, posture and balance dysfunctions by choosing proper assessment tools for PD. Patients at higher risk of falling must be referred for rehabilitation as early as possible, because antiparkinsonian drugs and surgery do not improve gait and posture in PD.

Key words: gait, cognition, Parkinson's disease, fall, gait assessment

RESUMO. Distúrbios da marcha e perda de controle postural são as causas principais de queda e incapacidade na doença de Parkinson (DP). A alteração cognitiva desempenha um papel importante para a perda do controle postural e aumenta o risco de quedas; ela também interfere no cuidado e tratamento dos distúrbios da marcha. É importante reconhecer os transtornos da marcha, postura e equilíbrio escolhendo instrumentos de avaliação adequados para identificar os pacientes que tem maior risco de quedas e referi-los para reabilitação o mais precocemente possível, porque os medicamentos e a cirurgia não melhoram a marcha, nem a postura de pacientes com DP.

Palavra-chave: marcha, cognição, doença de Parkinson, queda, avaliação da marcha.

INTRODUCTION

Patients with Parkinson disease's (PD) experience 62% more falls than patients with other neurological diseases. Falls are correlated with multiple factors, including postural, gait and cognitive dysfunction. Postural control and gait dysfunction may occur in early stages of PD and are characterized by postural instability, reduced arm swing, shorter path length, and loss of disassociated arm and trunk movements during gait.

Postural control requires the integration of three systems: visual, somatosensory and vestibular; and adaptation to continuous environmental changes.[1] However, this control may be disrupted by concurrent performance of a cognitive or another motor task.[2] According to Hausdorff et al.,[3] attention deficits lead to major changes in gait variability and stability. When PD patients accomplish a predetermined combined gait task, they are more likely to reduce walking speed and stride length and exhibit more freezing episodes, compared to performing single tasks. Single tasks are controlled by the basal ganglia, which are affected in PD. Dual tasks activate the frontal brain area and require voluntary/ conscious control.[4]

Postural balance is not a static condition, but a dynamic activity that requires constant neuromuscular responses.[5] This also holds true both in resting posture and while moving the body, e.g. walking, which involves shifting the center of gravity. Environmental demands must be identified by processing sensory inputs.[6]

Balance disturbances result from shifts in the center of gravity which may have an internal (e.g. natural oscillation of the body, limb movement) or external (a sudden push or braking car) origin. In this context, when there are deficits in the interpretation and integration of sensory systems, in planning the right responses or in the recruitment of the correct muscles to keep the center of gravity within the support base limits, the individual becomes susceptible to falls.[5,7]

The interaction between sensory, cognitive and motor systems is very important in PD patients. The disease can disrupt all these systems and, consequently, increase the risk of falls.[8,9] Postural instability is a motor manifestation of multiple causes and decreases the quality of life of PD patients. Also, it is not easily treatable by antiparkinsonian drugs and/or surgery.[10,11] Christofoletti et al.[9] investigated which factors are important predictors of gait disturbance and reduced mobility and noted that the major predictor of disability was poor postural balance.

Cognitive impairment, often manifested initially as executive dysfunction, affects both integration of sensory information and the motor planning required for maintaining balance, especially in dynamic activities such as walking.[12]

Therefore, appropriate assessment of gait and balance impairments are imperative and should also include the evaluation of executive function. Detection of cognitive and gait disturbances in PD patients may improve the quality of life of this population and reduce their risk of falls by earlier intervention and adequate therapeutic strategies.

POSTURE AND GAIT MOTOR ASSESSMENT IN PD

There are several rating scales, questionnaires, and timed tests that assess posture, gait and balance of PD patients, but few include more complex tasks that reflect environmental demands. We recommend careful choice of measurement instruments and the association of two or more tests for better evaluation of PD gait and balance.[7,8,13] Table 1 summarizes the instruments outlined below.

Table 1. Questionnaires, Instruments and Clinical Tests for Balance and Posture Assessment in PD.

Questionnaire/Instrument/Clinical Test	Domain
1. Static and Dynamic Computerized Posturography	Static and Dynamic Balance/Posture
1a. Dynamic Computerized Posturography	Dynamic Balance/Posture
1b. Sensory Organization Test (SOT)	Static Balance/Posture
1c. Multidirectional body movements on force platform	Dynamic Balance
1d. Balance Master System	Dynamic Balance
2. Timed Up and Go test	Gait (rising, walking, turning)
3. Berg Balance Scale	Static and Dynamic Balance
4. MiniBESTest	Static and Dynamic Balance/Gait

The assessment of static and dynamic balance, with or without the association of a cognitive task, is of great importance. Computerized posturography is an exam that assesses, using a force platform, the reaction forces that the body exerts on the ground and the trajectory of the center of pressure (COP). The information provided indicates the patient’s neuromuscular responses under the several conditions cited above. This technology can be used under different conditions, e.g. open eyes, visual and/or vestibular deprivation, narrow base of support and with a cognitive or motor task concomitantly.

Several studies have sought to elucidate the static balance of PD patients using posturography technology, but results remain controversial.[14-17] Some authors reported that PD patients show higher COP oscillation compared with age-matched healthy volunteers. Other authors have shown that PD patients oscillated less or within the same range as the control group. It is difficult to compare these studies since they have employed different methodologies concerning PD staging, freezing frequency, falls history, measurement instruments, variables and tasks.[10,18,19]

Nevertheless, more studies seem to agree that, in the presence of sensory disturbances, patients with PD have higher COP sway, and, consequently, greater postural instability.[8,10,20-22] A recent study by our group10 found that PD patients oscillated more than controls even under basal condition (open eyes). However, this oscillation was higher when the patient experienced vision deprivation. Static balance was also assessed under dual task conditions, in a standing position, and with a verbal fluency task. We noted that the association of the cognitive task resulted in higher disruption of balance compared to sensory disturbance without the association of a cognitive task. These results were consistent with the findings of Marchese et al.[23] The authors associated the standing position with a cognitive task (subtraction), comparing to baseline and to a dual motor task (standing and performing a finger sequence simultaneously). Fernandes et al.[22] published a similar study and replicated these results. They demonstrated that a cognitive task exposed the patient to greater instability, even in static postures.

While this effect has been seen under static posture conditions, higher cognitive demands, such as verbal fluency, arithmetic or an activity that requires more complex motor planning, can also influence performance on dynamic balance tasks.[7] Dynamic posturography measures how patients respond to mechanical or sensory disturbances. It is possible to identify responses during a predetermined task, assessing motor skills and balance, or only observing responses to external disturbance. The assessment of postural instability represents a major challenge for science, because it includes several complex systems. When sensory integration is altered, and/or cognitive function is impaired, motor responses become ineffective, leading to postural control dysfunction.[24]

The Sensory Organization Test (SOT) is a postural control assessment method. It entails the manipulation of visual, vestibular and proprioceptive neuromuscular information and evaluates how these systems respond. It is composed of six conditions for the triad of balance: vestibular, multisensory or physiological abnormalities. This technique involves tilting the surface or the visual surroundings under six conditions. The first three conditions provide a basic measurement of stability, standing with eyes open or closed on a static force plate surface, with visual surroundings moving or fixed. In conditions four to six, the patient experiences the disruption of somatosensory information, with a moving platform surface.[25]

The use of SOT in association with the MiniBESTest can identify 47% more deficits in anticipatory postural control, postural responses and gait, and sensory integration than the use of SOT assessment alone. This finding suggests the importance of retaining posturographic methods to evaluate balance.[7]

Another possibility for assessing dynamic stability is by evaluating responses after platform surface movements. It is possible to analyze COP displacement (as in static posturography) and assess ankle and hip balance strategies, integrated with electromyography. In one study, dynamic testing showed a decrease in the number of falls with increased sensorimotor strategies in 12 patients after bilateral deep brain stimulation (DBS) of the subthalamic nucleus.[26] It was also confirmed that trunk movements and muscle activity were equally present in PD patients and age-matched controls. However, in the PD group, leg muscle responses, and also medial deltoid and masseter activities were increased.[27]

Dynamic posturography measures balance while the patient is standing on a platform with a cylindrical base of support. The main objective of this method is to continuously compensate self-induced disturbances. One study showed that patients with poor performance in functional balance tests also had higher body sway and poorer reactive postural responses on posturography compared to patients that had normal adjustments on the pull test, which denoted a close relationship between clinical tests and posturography.[16]

Multidirectional body movements on the force platform is another useful technique for assessing the risk of falls in PD. In one study, patients stood on a fixed platform surface and moved their body in several directions, without stepping, following the directions established by the computer screen monitor, known as Limit of Stability (LOS). Patients with a history of falls had lower reaction time and velocity. The performance on LOS was correlated with the performance on functional tests, including the Unified Parkinson Disease Rating Scale, Timed Up and Go test, and Berg Balance Scale (BBS).[17]

The Balance Master System is a computerized posturography instrument designed for balance assessment. It evaluates body oscillations under different conditions (in orthostatic position to assess the LOS, SOT, to perform tasks related to daily activities and movement skills: sit-to-stand, tandem walk, turn, step over a box). It is also possible to develop a training sequence for therapeutic purposes to challenge patient’s limitations. Abilities requiring strength, balance, mobility and cognitive processing to perform certain tasks, such as stepping over, are a challenge for PD patients.[28,29]

The Timed Up and Go test is an appropriate tool for assessment of functional mobility and focuses more on executive function, compared to the BBS and Dynamic Gait Index (DGI) questionnaires.[31] TUG measures the time required to perform a sequence of activities, including the sit-to-walk, transfer, straight walking, turning and the walk-to-sit. The Dual task TUG has been shown as a good assessment for measuring gait and executive function. According to Christofoletti et al.,[32] the performance of PD patients is influenced by dual tasks, when the ability to adapt to environmental changes is affected.

The Berg Balance Scale is widely used to assess dynamic and static balance in elderly populations.[33] BBS is extensively used to assess balance in PD patients, with good validity and reproducibility. However, in some cases, high scores on BBS do not assure normal gait parameters in dual tasks, nor the absence of freezing.

The MiniBESTest[34] assesses balance using 14 tasks including the TUG, Push and Reach test, gait speed, negotiating obstacles, and turning. According to Mak et al.,[35] scores lower than 19 are good predictors of recurrent and future falls in PD patients.

The choice of proper clinical balance assessment instruments and their association with static and/or dynamic postural tests contributes to better identification of patients with higher risk of falls. But which tests should be chosen? Bloem et al.[36] reviewed many clinical tests for the Movement Disorders Society Rating Scales Committee. Although there are several instruments that adequately assess freezing of gait and balance confidence in PD, most clinical rating scales for gait, balance, and posture perform suboptimally. The authors recommend future development of a PD-specific, easilyadministered, comprehensive gait and balance scale that separately assesses all relevant constructs with good clinimetric properties.

THE INFLUENCE OF EDUCATION IN PD

The concept of an education-augmented cognitive reserve has been extensively investigated in studies focusing on dementia, normal aging, and PD.[37] However, few studies have explored the relationship between education and motor outcomes. The possible mechanisms that might explain this relationship include: (1) greater education-associated cerebral volumes that are more resilient to neurodegenerative changes; (2) more efficient recruitment of alternative brain networks that may be used for neurological function; or (3) enhanced brain repair/recovery mechanisms.[37]

Kotagal et al.[38] conducted a cross-sectional clinical imaging study of 142 subjects with PD. All subjects underwent [^{11}C] dihydrotetrabenazine PET to confirm nigrostriatal dopaminergic denervation and also brain MRI to estimate adjusted cortical gray matter volume (GMV). After adjusting for possible confounders, including cognitive and dopaminergic covariates, as well as nonspecific neurodegeneration covariates (age, disease duration, and total adjusted cortical GMV), lower years of education remained a significant predictor of higher total MDS-UPDRS motor scores. Educational level was inversely associated with white matter (WM) hyperintensities. Higher educational attainment is associated with lower severity of motor impairment in PD, and this association may reflect an extranigral protective effect upon WM integrity.

These results are also consistent with previous studies that have shown inverse correlations between balance performance in PD and educational attainment.[39,40]

Souza et al.[40] investigated the influence of educational status (number of years of formal education) on executive function tasks and balance. PD patients and healthy elderly controls were asked to perform the Trail Making Test (TMT) and BBS.

Participants with lower educational status (both PD and control groups) performed worse on the TMT Part B than those with higher educational status. Within the PD group, the less-educated patients scored worse on the BBS than the more-educated group. This finding may be attributed to higher cognitive reserve in those patients with PD who had more years of formal education.

Cognitive enrichment fosters the development of neuroplasticity, which permits the maintenance of cognitive function even in a person with brain pathology. Cognitive resources, such as visual perception, memory, divided attention, coordination, motor sequencing, and executive function, help to reduce the risk of falls and to compensate for balance impairment in older adults.[41,42]

Voos et al.[41] demonstrated that, in healthy elderly people, both poor executive function performance (assessed by the TMT) and Low Educational Status (assessed by self-reported years of formal education) may be related to lower functional balance scores on BBS. According to the literature, the influence of formal education on executive function is well established.[39-43] If educational status influences the development of executive function during lifespan, and executive function is related to balance and gait,[43-45] it follows that educational status may also have some influence on balance and gait.

CHOLINESTERASE INHIBITOR AND PD GAIT

The pedunculopontine nucleus (PPN) is located in the caudal mesopontine tegmentum and provides the majority of cholinergic inputs to the thalamus, with projections to the striatum, cerebellum, and brainstem. It also has connections with the basal ganglia nuclei, specifically the substantia nigra, subthalamic nucleus, and globus pallidus interna. The PPN and nucleus basalis of Meynert degenerate in PD and the cholinergic loss is associated with cognitive impairment. PD dementia and dementia with Lewy Bodies present fluctuation in conciousness, which can be improved by cholinesterase inhibitors (CI). This fact suggests that cholinergic loss participates in the cognitive spectrum associated with Lewy body deposition and α-synuclein accumulation.[46]

Falls are related to cognition and may be caused by similar neurochemical disturbances. Evidence from imaging studies supports the idea that degeneration of the cholinergic system in PD may be responsible for a number of motor and non-motor symptoms, including cognitive dysfunction, depression, falls and postural instability. Moreover, cholinergic degeneration may also be associated with gait dysfunction. Greater postural instability, which is related to falls, is correlated with worse scores on tests associated with attention and executive function. The interaction between attention and gait may be observed during dual tasking and is endorsed by reports of CI reducing the risk of falls in PD patients.[46]

In animal models, cholinergic–striatal disruption of attentional–motor pathways in the basal forebrain is a major cause of falls. The association between cortical and subcortico-mesencephalic cholinergic deficits in patients with PD without dementia with high-level gait disorders (such as freezing of gait), postural instability, falls, coupled with dysexecutive syndrome and apathy, require further research.[47]

Gait speed in PD is also correlated with cholinergic function. Bohnen et al.,[48] observed that a PD subgroup with preserved cortical cholinergic innervations displayed no significant slowing of gait speed compared with non-PD control subjects. The multisystem hypocholinergic effect on gait speed was driven by basal forebrain but not by PPN-thalamic denervation effects, and the latter is associated with postural control. Alterations in cognitive function are linked to gait disturbances, while gait speed reduction predicted cognitive decline in initially unimpaired older adults. According to the authors, the mechanism of slowing of gait in PD can be conceptualized as a clinical state, in which preattentive striatal degradation is initially supplemented by increasing cognitive control mediated by cortical cholinergic mechanisms. As compensatory cholinergic systems degenerate, gait speed is reduced.

Recent trials with high-dose rivastigmine in nondemented PD patients indicated that the drug can improve gait stability and might reduce the frequency of falls. However, the drug had no significant effects on episodes of freezing of gait or on the neuropsychological outcomes assessed.[49] This finding contradicts a previous meta-analysis conducted by Pagano et al.,[50] in which CI proved an effective treatment for cognitive impairment in patients with PD but failed to reduce the risk of falls. This class of medications impacted positively on global assessment and behavioral disturbance without significantly affecting motor function scales. In fact, an earlier double-blind, placebo-controlled study of PD patients with pre-dementia apathy showed that rivastigmine treatment was associated with a lower overall apathy score and caregiver burden, as well as greater intellectual curiosity and action initiation.[51]

Future trials might answer the question of how falls relate to cholinergic and attention function. Many researchers have investigated the effect of PPN stimulation in PD patients because of previous reports of motor benefits. Mestre et al.[52] reported their result of longterm unilateral PPN DBS and showed an initial benefit of PPN stimulation for PD gait-related symptoms but after 4 years this improvement was not sustained. The authors highlighted some limitations to their findings including technical issues and outcome assessment. However, to what extent does degeneration of PPN cholinergic neurons affect gait disturbances in PD? Moreover, the correlations between the various patterns of cholinergic denervation and clinical phenotypes in PD have not been studied.

IMPLICATIONS FOR REHABILITATION IN PD

Nocera et al.[30] conducted a study in which PD patients performed a 10-week home exercise program targeting abdominal muscles. The program included squats, calf raises, and step-up exercises. The authors showed significant improvement in four to six SOT conditions, with unstable surface in eyes open and closed conditions. Patients improved balance with home exercise, contributing to maintaining postural stability and reducing the risk of falls. Therefore, focusing on motor training can also improve dual-task performance and balance.

The dual task can influence and, consequently, the risk of falls in PD patients. Firstly, there was the assumption that when the patient performed two simultaneous cognitive and motor tasks, performance would be impaired and there would be an increase in the number of falls. Therefore, such situations were avoided in therapy sessions. However, recent studies have shown that the subcomponents of these activities can serve as cues, helping patients in their locomotion. Mirelman et al.[53] trained PD patients on a treadmill associated with virtual reality. They found a positive impact when patients performed both training tasks simultaneously, with decreased risk of falls and greater gait stability. This result favors dual task training in PD patients.

Plotnik et al.[54] demonstrated that cognitive-motor complexity act together to control gait in PD patients suffering from fluctuations in motor responses. There was a pronounced effect of dual task conditions on gait variability, asymmetry and bilateral coordination. Other studies report that there is improvement of mobility and cognitive function, as well as a reduction in the risk of falls, when motor and cognitive activities are integrated. These affirmations emphasize the importance of dualtask training and the development of gait rehabilitation programs. Moreover, dual tasks are part of our activities of daily living.[55,56]

Strategies to improve gait depend on the ability to use attention and mental images, which rely on cognitive ability. These strategies include visual and auditory cues.[57] Recent studies show the benefits of these cues for decreasing the risk of falls and reinforce the hypothesis that patients with PD require more attention for motor task performance.

In conclusion, rehabilitation contributes to the improvement of gait and falls prevention. When using the cues, there is explicit, semantic and episodic memory (declarative) demand to compensate for the loss of the implicit memory, which is affected in PD. Many studies have also shown benefits of combined cueing (auditory and visual cues). Positive motor impact has been observed in gait parameters (length, time and cadence).[58]

Author contribution. Alessandra Ferreira Barbosa: writing the manuscript, critical revision, approval of the final version of the manuscript; Janini Chen: writing the manuscript, critical revision, approval of the final version of the manuscript; Fernanda Freitag: writing the manuscript, approval of the final version of the manuscript; Debora Valente: writing the manuscript, approval of the final version of the manuscript; Carolina de Oliveira Souza: writing the manuscript, approval of the final version of the manuscript; Mariana Callil Voos: writing the manuscript, critical revision, approval of the final version of the manuscript; Hsin Fen Chien: conception and design, writing the manuscript, critical revision, approval of the final version of the manuscript

REFERENCES

1. Stolze H, Klebe S, Zechlin C, Baecker C, Friege L, Deuschl G. Falls in frequent neurological diseases--prevalence, risk factors and aetiology. J Neurol. 2004;251:79-84.

2. Mak MK. Reduced step length, not step length variability is central to gait hypokinesia in people with Parkinson's disease. Clin Neurol Neurosurg 2013;115(5):587-90.

3. Hausdorff JM, Balash J, Giladi N. Effects of cognitive challenge on gait variability in patients with Parkinson's disease. J Geriatr Psychiatry Neurol. 2003;16(1):53-8.

4. Brauer SG, Woollacott MH, Lamont R, Clewett S, O'Sullivan J, Silburn P, Mellick GD, Morris ME. Single and dual task gait training in people with Parkinson's disease: a protocol for a randomised controlled trial. BMC Neurol. 2011 27;11:90.

5. Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? Age Ageing. 2006;35:7-11.

6. Brooke-Wavell K, Perrett LK, Howarth PA, Haslam RA. Influence of the visual environment on the postural stability in healthy older women. Gerontology. 2002;48(5):293-7.

7. Gera G, Freeman DL, Blackinton MT, Horak FB, King L. Identification of Balance deficits in people with Parkinson Disease; is the Sensory Organization Test Enough? Int J Phys Med Rehabil. 2016;4(1). pii: 322.

8. Rossi M, Soto A, Santos S, Sesar A, Labella T. A Prospective Study of Alterations in Balance among Patients with Parkinson's Disease. European Neurology. Eur Neurol. 2009;61(3):171-6.

9. Christofoletti G, McNeely ME, Campbell MC, Duncan RP, Earhart GM. Investigation of factors impacting mobility and gait in Parkinson disease. Hum Mov Sci. 2016;49:308-14.

10. Barbosa AF, Souza C de O, Chen J, Francato DV, Caromano FA, Chien HF, et al. The competition with a concurrent cognitive task affects posturographic measures in patients with Parkinson disease. Arq Neuropsiquiatr. 2015;73(11):906-12.

11. Lawson RA, Yarnall AJ, Duncan GW, Breen DP, Khoo TK, WilliamsGray CH, et al. Cognitive decline and quality of life in incident Parkinson's disease: The role of attention. Parkinsonism Relat Disord. 2016;27:47-53.

12. Lord S, Rochester L, Hetherington V, Allcock LM, Burn D. Executive dysfunction and attention contribute to gait interference in 'off' state Parkinson's Disease. Gait Posture. 2010;31(2):169-74.

13. Doná F, Aquino CC, Gazzola JM, Borges V, Silva SM, Ganança FF, et al. Changes in postural control in patients with Parkinson's disease: a posturographic study. Physiotherapy. 2016;102(3):272-9.

14. Horak FB, Nutt JG, Nashner LM. Postural inflexibility in parkinsonian subjects. J Neurol Sci. 1992;111(1):46-58.

15. Frenklach A, Louie S, Koop MM, Bronte-Stewart H. Excessive Postural Sway and the Risk of Falls at Different Stages of Parkinson's Disease. Mov Disord. 2009;24(3):377-85.

16. Ebersbach G, Gunkel M. Posturography reflects clinical imbalance in Parkinson's disease. Mov Disord. 2011;26(2):241-6.

17. Johnson L, James I, Rodrigues J, Stell R, Thickbroom G, Mastaglia F. Clinical and posturographic correlates of falling in Parkinson's disease. Mov Disord. 2013;28(9):1250-6.

18. Fioretti S, Guidi M, Ladislao L, Ghetti G. Analysis and reliability of posturographic parameters in Parkinson patients at an early stage. Conf Proc IEEE Eng Med Biol Soc. 2004;1:651-4.

19. Rocchi L, Chiari L, Cappello A, Horak FB. Identification of distinct characteristics of postural sway in Parkinson's disease: A feature selection procedure based on principal component analysis. Neurosci Lett. 2006;394(2):140-5.

20. Ickenstein GW, Ambach H, Klöditz A, Koch H, Isenmann S, Reichmann H, Ziemssen T. Static posturography in aging and Parkinson's disease. Front Aging Neurosci. 2012;4:20.

21. Lee JM, Koh SB, Chae SW, Seo WK, Kwon DY, Kim JH, et al. Postural Instability and Cognitive Dysfunction in Early Parkinson's Disease. Can J Neurol Sci. 2012;39(4):473-82.

22. Fernandes A, Sousa AS, Couras J, Rocha N, Tavares JM. Standing balance in individuals with Parkinson's disease during single and dualtask conditions. Gait Posture. 2015;42(3):323-8.

23. Marchese R, Bove M, Abbruzzese G. Effect of cognitive and motor tasks on postural stability in Parkinson's disease: A posturographic study. Mov Disord. 2003;18(6):652-8.

24. Furman JM, Baloh RW, Barin K, Hain TC, Herdman S, Horst RK, Parker SW. Assessment: posturography. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology Neurology. 1993;43(6):1261-4.

25. Nashner LM. Computerized dynamic posturography. In G. P. Jacobson CW, Newman, & JM Kartush (Eds.), Handbook of balance function testing. San Diego, CA: Singular; 1993: 280-334.

26. Colnat-Coulbois S, Gauchard GC, Maillard L, Barroche G, Vespignani H, Auque J, Perrin PP. Bilateral subthalamic nucleus stimulation improves balance control in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2005;76(6):780-7.

27. Visser JE, Oude Nijhuis LB, Janssen L, Bastiaanse CM, Borm GF, Duysens J, Bloem BR. Dynamic posturography in Parkinson's disease: diagnostic utility of the "first trial effect". Neuroscience. 2010;168(2): 387-94.

28. NeuroCom International Inc. Instructions for use: Balance Master System operator's manual, Version 8.1, 2003.

29. Nocera JR, Horvat M, Ray CT. Impaired step up/over in persons with Parkinson's disease. Adapt Phys Activ Q. 2010;27(2):87-95.

30. Nocera J, Horvat M, Ray CT. Effects of home-based exercise on postural control and sensory organization in individuals with Parkinson disease. Parkinsonism Relat Disord. 2009; 15(10):742-5.

31. Herman T, Giladi N, Hausdorff JM. Properties of the 'timed up and go' test: more than meets the eye. Gerontology. 2011;57(3):203-10.

32. Christofoletti G, Andrade LP, Beinotti F, Borges G. Cognition and dualtask performance in older adults with Parkinson's and Alzheimer's disease. Int J Gen Med. 2014;7:383-8.

33. Berg KO, Wood-Dauphinee SL, Williams JI, Maki B. Measuring balance in the elderly: validation of an instrument. Can J Public Health. 1992;83 Suppl 2:S7-11.

34. Franchignoni F, Horak F, Godi M, Nardone A, Giordano A. Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. J Rehabil Med. 2010;42(4):323-31.

35. Mak MK, Auyeung MM. The mini-BESTest can predict parkinsonian recurrent fallers: a 6-month prospective study. J Rehabil Med. 2013;45(6):565-71.

36. Bloem BR, Marinus J, Almeida Q, Dibble L, Nieuwboer A, Post B, et al. Measurement instruments to assess posture, gait, and balance in Parkinson's disease: Critique and recommendations. Mov Disord. 2016;31(9):1342-55.

37. Scarmeas N, Stern Y. Cognitive reserve: implications for diagnosis and prevention of Alzheimer's disease. Curr Neurol Neurosci Rep. 2004;4:374-380.

38. Kotagal V, Bohnen NI, Muller M, Koeppe RA, Frey KA, Langa KM, Albin RL. Educational Attainment and Motor Burden in Parkinson's Disease. Mov Disord. 2015;30:567-71.

39. Souza C de O, Voos MC, Fonoff FC, et al. Relation between educational status and motor scales (UPDRS-III, Berg Balance Scale and time Up and Go Test) in individuals with Parkinson's disease. Mov Disord. 2012;Suppl 1:328.

40. Souza C de O, Voos MC, Francato DV, Chien HF, Barbosa ER. Influence of educational status on executive function and functional balance in individuals with Parkinson disease. Cogn Behav Neurol. 2013;26:6-13.

41. Voos MC, Custodio EB, Malaquias M Jr. Relationship of executive function and educational status with functional balance in older adults. J Geriatr Phys Ther. 2011;34:11-18.

42. Yogev S, Hausdorf JM, Giladi N. The role of executive function and attention in gait. Mov Disord. 2008;23:329-42.

43. Tun PA, Lachman ME. Age differences in reaction time and attention in a national telephone sample of adults: education, sex, and task complexity matter. Dev Psychol. 2008;44:1421-9.

44. Van Iersel MB, Kessels RPC, Bloem BR, Verbeek AL, Olde Rikkert MG. Executive functions are associated with gait and balance in communityliving elderly people. J Gerontol. 2008;63:1344-9.

45. Hirota C, Watanabe M, Tanimoto Y, Kono R, Higuchi Y, Kono K. A crosssectional study on the relationship between the Trail Making Test and mobility- related functions in community-dwelling elderly. Nippon Ronen Igakkai Zasshi. 2008;45:647-54.

46. Yarnall A, Rochester L, Burn DJ. The interplay of cholinergic function, attention, and falls in Parkinson's disease. Mov Disord. 2011;26(14): 2496-503.

47. Moreau C, Devos D, DefebvreL. Acetylcholinesterase inhibitors and gait: a steadying hand? Lancet Neurol. 2016;15(3):232-3.

48. Bohnen NI, Frey KA, Studenski S, Kotagal V, Koeppe RA, Scott PJ, et al. Gait speed in Parkinson disease correlates with cholinergic degeneration. Neurology. 2013;81(18):1611-6.

49. Henderson EJ, Lord SR, Brodie MA, Gaunt DM, Lawrence AD, Close JC, et al. Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol. 2016;15(3):249-58.

50. Pagano G, Rengo G, Pasqualetti G, Femminella GD, Monzani F, Ferrara N, Tagliati M. Cholinesterase inhibitors for Parkinson's disease: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2015;86(7):767-73.

51. Devos D, Moreau C, Maltête D, Lefaucheur R, Kreisler A, Eusebio A, et al. Rivastigmine in apathetic but dementia and depression-free patients with Parkinson's disease: a double-blind, placebo-controlled, randomized clinical trial. J Neurol Neurosurg Psychiatry. 2014;85(6): 668-74.

52. Mestre TA, Sidiropoulos C Hamani C, Poon YY, Lozano AM, Lang AE, Moro E. Long-term double-blinded unilateral pedunculopontine area stimulation in Parkinson's disease. Mov Disord. 2016;31(10):1570-4.

53. Mirelman A, Maidan I, Herman T, Deutsch JE, Giladi N, Hausdorff JM. Virtual Reality for Gait Training: Can It Induce Motor Learning to Enhance Complex Walking and Reduce Fall Risk in Patients With Parkinson's Disease? J Gerontol A BiolSci Med Sci. 2011;66A(2):234-40.

54. Plotnik M, Giladi N, Dagan Y, Hausdorff JM. Postural instability and fall risk in Parkinson's disease: impaired dual tasking, pacing, and bilateral coordination of gait during the ''ON'' medication state. Exp Brain Res. 2011;210:529-38.

55. Mirelman A, Rochester L, Reelick M, Nieuwhof F, Pelosin E, Abbruzzese G, et al. V-TIME: a treadmill training program augmented by virtual reality to decrease fall risk in older adults: study design of a randomized controlled Trial. BMC Neurology. 2013;13:15.

56. Wild LB, Lima DB, Balardin JB, Rizzi L, Giacobbo BL, Oliveira HB, et al. Characterization of cognitive and motor performance during dual-tasking in healthy older adults and patients with Parkinson's disease. J Neurol. 2013;260:580-9.

57. Iansek R, Danoudis M, Bradfield N. Gait and cognition in Parkinson's disease: implications for rehabilitation. Rev Neurosci. 2013;24(3): 293-300.

58. Nanhoe-Mahabier W, Delval A, Snijders AH, Weerdesteyn V, Overeem S, Bloem BR. The possible price of auditory cueing: influence on obstacle avoidance in Parkinson's disease. Mov Disord. 2012;27(4):574-8.

ANEXO 4 – Avaliação da Fluência Verbal

TESTE DE FLUÊNCIA VERBAL

"O senhor deve falar todos os nomes de animais de que se lembrar, o mais rápido possível. Quantos mais você falar, melhor. Pode começar". Anote os nomes de animais falados pelo/a idoso/a a cada 15 segundos (use o cronômetro e guie-se pelos relógios indicadores que aparecem abaixo para anotar as respostas do/a idoso/a).

□____
____

□____
____

□____
____

□____
____

ESCORE(número de animais lembrados em 1 minuto): _______

TESTE DE FLUÊNCIA FONÊMICA (LETRA F)

Instruções: "O senhor deve falar todas as palavras que se lembrar que se iniciam com a letra F, em um minuto, Mas não vale nome de pessoas, nome de lugares ou palavras parecidas como casa, casinha e casarão. As palavras devem iniciar com a letra F. Quantos mais você falar, melhor, fale o mais rápido possível!!! "Pode começar". Anote os nomes de animais falados pelo/a idoso/a a cada 15 segundos (use o cronômetro e guie-se pelos relógios indicadores que aparecem abaixo para anotar as respostas do/a idoso/a).

□____
____

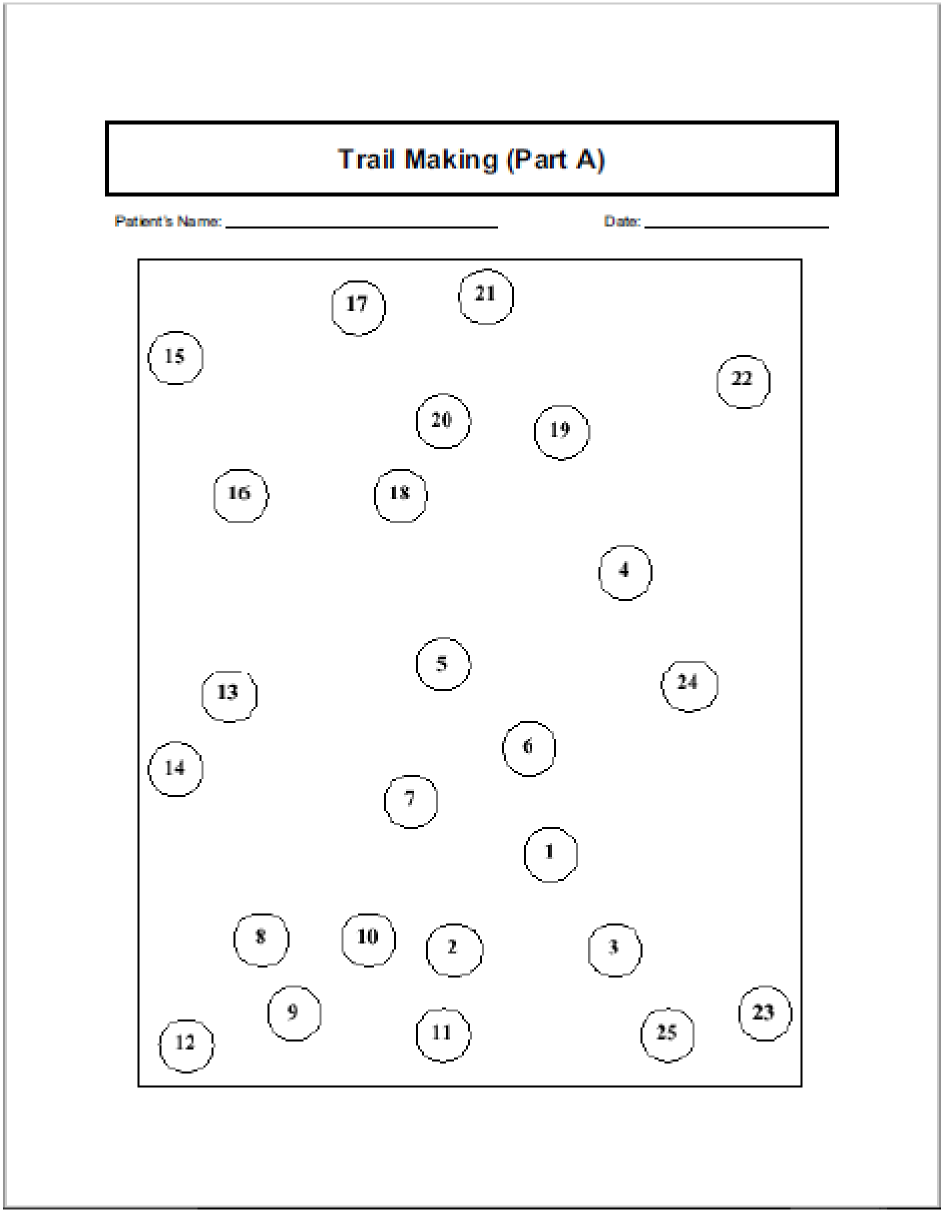
□____
____

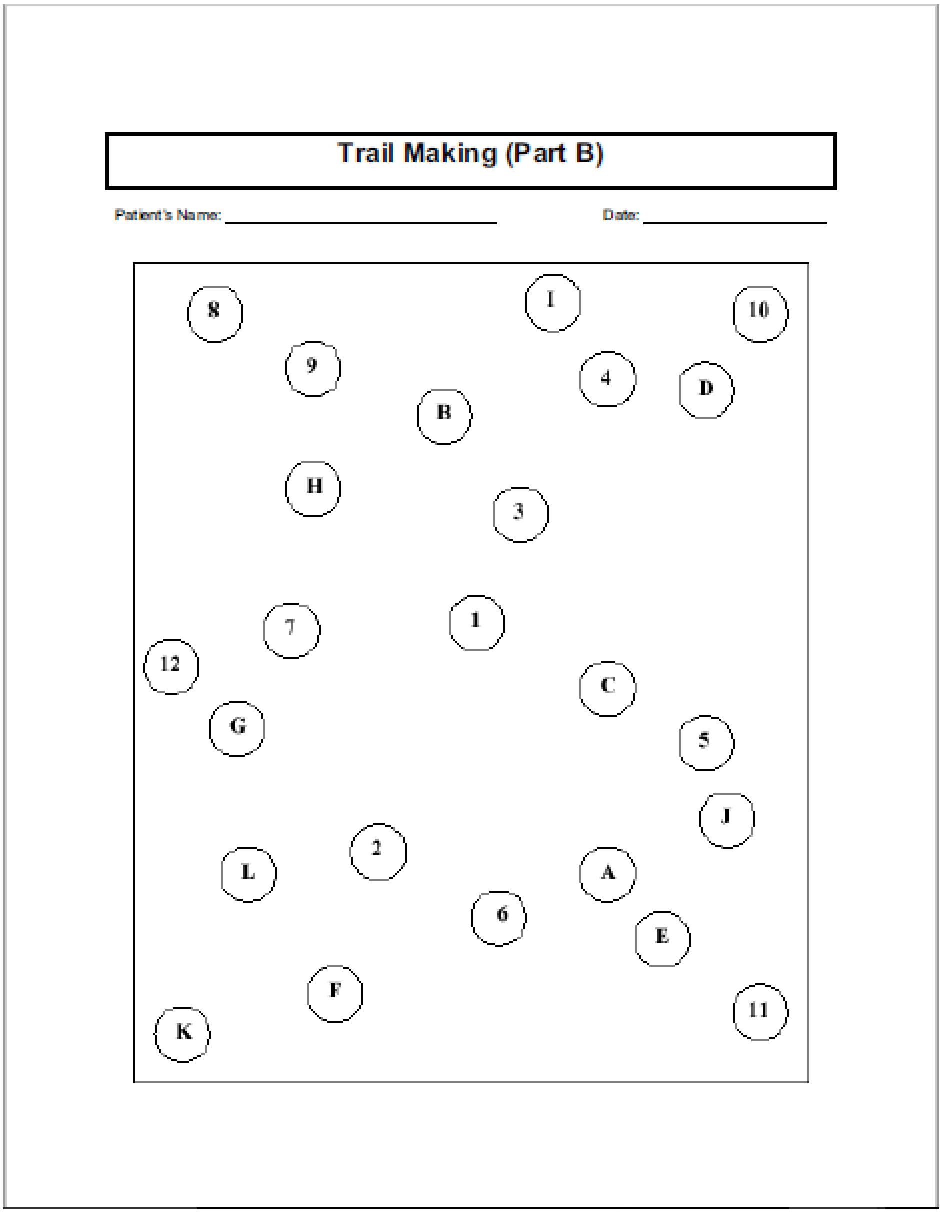
□____
____

□____
____

ESCORE (número de animais lembrados em 1 minuto): _______

ANEXO 5 – Protocolo *Trail Making Test*





Trail Making (Part B)

Patient's Name: ______________________ Date: ______________

ANEXO 6 – Parecer da Plataforma Brasil e projeto de pesquisa

HC FMUSP

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA USP - HCFMUSP

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação da função executiva e da fluência verbal em paciente com doença de Parkinson

Pesquisador: Mariana Callil Voos

Área Temática:

Versão: 1

CAAE: 55948116.6.0000.0068

Instituição Proponente: HOSPITAL DAS CLINICAS DA FACULDADE DE MEDICINA DA U S P

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.631.497

Apresentação do Projeto:

O processo natural do envelhecimento se torna ainda mais relevante diante do aparecimento de algumas doenças com maior incidência entre os idosos, como cardiovasculares e neurológicas. As doenças neurodegenerativas estão nesse grupo, entre elas, as mais comuns são a doença de Alzheimer e a doença de Parkinson (DP). A DP não é incomum na população adulta, mas sua incidência aumenta na população idosa.

As alterações cognitivas presentes na DP, somadas aos déficits cognitivos característicos do envelhecimento, exacerbam as dificuldades e déficits funcionais desses indivíduos. Os sintomas somados ao processo de envelhecimento normal interferem no desempenho de diversas atividades de vida diária, principalmente as que envolvem dupla tarefa (motora e cognitiva). Um teste bastante utilizado para avaliação da função executiva nesses pacientes é o Trail Making Test (TMT), por envolver atividades motoras, cognitivas e cognitivo-motoras, porém ainda não é descrito dados normativos do teste para essa população.

Objetivo da Pesquisa:

O presente projeto tem como objetivo primário descrever dados normativos para o TMT para a população brasileira de pacientes com DP, comparando seu desempenho ao de idosos saudáveis.

Endereço: Rua Ovídio Pires de Campos, 225 5º andar
Bairro: Cerqueira Cesar **CEP:** 05.403-010
UF: SP **Município:** SAO PAULO
Telefone: (11)2661-7585 **Fax:** (11)2661-7585 **E-mail:** cappesq.adm@hc.fm.usp.br

Avaliação dos Riscos e Benefícios:

Risco mínimo, devidamente assinalado no TCLE.

Comentários e Considerações sobre a Pesquisa:

O estudo poderá trazer avanços ao conhecimento sobre a comunicação oral em pessoas com doença de Parkinson.

Considerações sobre os Termos de apresentação obrigatória:

Termos apresentados de forma adequada.

Recomendações:

Sem recomendações adicionais.

Conclusões ou Pendências e Lista de Inadequações:

Sem pendências .

Considerações Finais a critério do CEP:

Em conformidade com a Resolução CNS nº 466/12 – cabe ao pesquisador: a) desenvolver o projeto conforme delineado; b) elaborar e apresentar relatórios parciais e final; c)apresentar dados solicitados pelo CEP, a qualquer momento; d) manter em arquivo sob sua guarda, por 5 anos da pesquisa, contendo fichas individuais e todos os demais documentos recomendados pelo CEP; e) encaminhar os resultados para publicação, com os devidos créditos aos pesquisadores associados e ao pessoal técnico participante do projeto; f) justificar perante ao CEP interrupção do projeto ou a não publicação dos resultados.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_660808.pdf	10/05/2016 15:55:36		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_projetoAlessandra_correto.doc	10/05/2016 15:54:41	Mariana Callil Voos	Aceito
Outros	anexo_2_HCFMUSP.pdf	21/03/2016 21:01:28	Mariana Callil Voos	Aceito
Folha de Rosto	folha_de_rosto_projetoParkinson.pdf	21/03/2016 20:52:27	Mariana Callil Voos	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_plataformabrasil.docx	05/02/2016 15:51:45	Mariana Callil Voos	Aceito

Endereço: Rua Ovídio Pires de Campos, 225 5º andar
Bairro: Cerqueira Cesar **CEP:** 05.403-010
UF: SP **Município:** SAO PAULO
Telefone: (11)2661-7585 **Fax:** (11)2661-7585 **E-mail:** cappesq.adm@hc.fm.usp.br

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 11 de Julho de 2016

Assinado por:
Joel Faintuch
(Coordenador)

Projeto de Pesquisa

RESUMO

INTRODUÇÃO: A inversão da pirâmide etária é uma realidade em diversos países em desenvolvimento, inclusive no Brasil, que traz grandes impactos sociais, econômicos e na saúde por envolver o envelhecimento da população o que acarreta individualmente em alterações cognitivas (déficit de memória e desempenho em função executiva), e alterações físicas (diminuição do trofismo e tônus muscular, diminuição da densidade óssea, alterações posturais, déficit de equilíbrio e problemas na marcha). Também há o aumento da prevalência de algumas doenças principalmente as cardiovasculares e doenças neurodegenerativas, dentre elas a doença de Parkinson que afeta de 1,5 a 2% da população acima de 60 anos e é tipicamente caracterizada por distúrbios motores como o tremor de repouso, a rigidez muscular, a bradicinesia e a instabilidade postural, porém também são descritas algumas complicações incluindo déficits cognitivos. Esses sintomas somados ao processo de envelhecimento normal interferem no desempenho de diversas atividades de vida diária, principalmente as que envolvem dupla tarefa (motora e cognitiva). Um teste bastante utilizado para avaliação da função executiva nesses pacientes é o Trail Making Test (TMT), por envolver atividades motoras, cognitivas e cognitivo-motoras, porém ainda não é descrito dados normativos do teste para essa população. **OBJETIVOS:** Descrever dados normativos para o TMT para a população brasileira de pacientes com Parkinson, comparando seu desempenho ao de idosos saudáveis, verificar o efeito da escolaridade no desempenho do TMT em ambas as populações e verificar se há correlação entre o TMT e o teste de fluência verbal, outro teste muito utilizado na avaliação cognitiva. **MÉTODO:** Será realizado um estudo observacional transversal que contará com pacientes com Parkinson e idosos saudáveis de idade pareada. A avaliação contará com a aplicação do UPDRS-seção motora, o TMT e o teste de fluência verbal (palavras com F, frutas e animais). Serão realizadas ANOVAs para as comparações entre os grupos e o teste de correlação de Pearson para verificar possíveis relações ou associações entre o teste de fluência verbal e o TMT. **RESULTADOS ESPERADOS:** espera-se que os pacientes com Parkinson sejam mais lentos tanto no desempenho do TMT quanto na fluência verbal e que esse resultado seja influenciado pela escolaridade. Esperam-se correlações significativas entre o TMT e o teste de fluência verbal.

Palavras chave: Doença de Parkinson, envelhecimento, cognição, função executiva

1. INTRODUÇÃO

Há alguns anos vem sendo discutida a inversão da pirâmide etária, fenômeno visto no Brasil e em outros países em desenvolvimento. Muitos estudiosos têm se dedicado a entender os motivos e, principalmente, as implicações que o aumento do número de idosos pode causar em diversos domínios, como o social, econômico e também na saúde pública. Em um estudo sobre este fenômeno, Carvalho e colaboradores (2008) afirmam que o Brasil está entre os países com o ritmo mais acentuado de crescimento do quociente idosos-jovens e estimam que até 2025 deverão existir cerca de 46 idosos para cada 100 jovens, relação que, em 1970, era de 10 idosos para cada 100 jovens. É previsto também que o número de idosos ultrapasse o número de crianças até 2050.

É comum que, com o envelhecimento normal, surjam diversas alterações físicas, como a diminuição da densidade óssea (Kherad et al., 2015), do trofismo e tônus muscular (Gavin et al., 2014), aparecimento da rigidez articular e limitação de movimentos (DeVita; Hortobagyi, 2000), alteração de postura (Masaki et al., 2015), equilíbrio e marcha (Voos *et al*., 2011). Além dessas alterações, que isoladas já poderiam afetar a qualidade de vida, há também alterações cognitivas, como queda do desempenho em função executiva, perda de memória e da fluência verbal, que aumentam as dificuldades vividas no envelhecimento (Voos, 2010; Voos et al., 2014).

Uma forma comum e bem simples de verificar a integridade cognitiva é por meio de testes de fluência verbal, que avaliam a função executiva, a linguagem e a memória semântica (Brucki; Rocha, 2004). Esses testes têm se mostrado alterados em idosos saudáveis (IS) (Kempler et al., 1998; Acevedo et al., 2000), principalmente nos de baixa escolaridade (Brucki; Rocha, 2004). Porém, observa-se prejuízo ainda maior em indivíduos com quadros patológicos, como a doença de Parkinson (DP) (Araujo et al., 2011; Henry; Crawford, 2004). No teste geralmente é solicitado que o paciente nomeie o máximo de palavras possíveis, em 60 segundos, iniciando com uma determinada letra (mais comumente F, A ou S), ou nomeando palavras de uma determinada categoria, como animais (Brucki; Rocha, 2004). A pontuação é feita considerando o número de palavras faladas, o número de palavras de cada 15 segundos, o número de categorias utilizadas, a troca de categorias e o agrupamento.

Em uma revisão de literatura sobre a influência da escolaridade no desempenho e no aprendizado de tarefas motoras, Voos *et al*. (2014) descreveram que o desempenho em função executiva encontra-se prejudicado em idosos, dado ainda mais relevante em população de baixa escolaridade, como a brasileira. O quadro apresentado nesse estudo, com dados que apoiam esses resultados, está apresentado na Tabela 3.

Tabela 3: Tabela do artigo de revisão de literatura sobre a influência da escolaridade no desempenho e no aprendizado de tarefas motoras (Voos et al. 2014)

Authors (year)	Number of subjects	Age (years)	School education (years)	Tasks	Results
1. Souza *et al.*[34] (2013)	28 patients with Parkinson's disease 30 healthy elderly	60-80	G1:4-10 G2: 12-18	Berg's balance scale and trail making test	Elderly with LSE present worse performance on trail test; among individuals with Parkinson's disease, schooling impaired more than Just balance
2. Yong e Saito[41] (2012)	4968	≥65	G1: ≤8 G2: >8	Ability to perform daily living activities	Individuals with LSE have less years of active life (with functional independency)
3. Machado *et al.*[24] (2011)	30	20-59	G1: 1-5 G2: >10	Taking alternate steps from the ground to a platform (simple task) and identifying images on a screen (double task)	Individuals with LSE make more mistakes in visuals tasks, take less steps in motor tasks and have worse performance in double tasks
4. Gregory *et al.*[42] (2011)	436	70 a 79	G1: 0-8 G2: 9-11 G3: 12 G4: >12	Walking half a mile, climbing up steps, doing chores, getting up from bed and from a chair	Pessoas com EB têm mais risco de apresentar dificuldades nas tarefas avaliadas. EB é um preditor independente de dificuldades de mobilidade em nível pré-clínico
5. Hong *et al.*[17] (2011)	125	≥65	G1: IL G2: L	Copying overlapped pentagons and a cube	Idosos NA apresentam pior desempenho
6. Voos *et al.*[35] (2011)	101	60-80	3-16	Berg's balance scale and timed rising up and walking	Idosos com EB apresentam pior desempenho
7. Voos[39] (2010)	70	G1: 20-34 G2: 50-64 G3: 65-79	G1: ≤11 G2: ≥12	Ambulate as soon as possible on mats in a path formed by numbers (part A) and letters (part B)	Individuos mais idosos e com EB apresentam mais dificuldade (menor velocidade), sobretudo an parte B
8. Kim e Chey[18] (2010)	240 (healthy), 28 (mild dementia)	G1: 55-64 G2: 65-74 G3: 75-84	G1: ≤6 G2: ≥7	Performing the clock test	Escolaridade e doença influenciam no desempenho. Individuos com EB apresentam desempenho semelhante ao de individuos com demência leve
9. Walker *et al.*[32] (2009)	100 (with brain injury)	16-75	0-12	Completing figures, codes, cubes, matrices, arranging figures, looking for symbols ans setting up objects	Pior desempenho para os mais idosos e com EB
10. Ashendorf *et al.*[19] (2009)	307	55-74	G1: ≤12 G2: >12	Task of opposing fingers and Groowed pegboard test	A tarefa de oposição de dedos sofre influência da escolaridade (individuos com EB: pior desempenho), mas o *grooved pegboard test* não

11. Meijer *et al.*[45] (2009)	1344	G1: 24-47 G2: 49-77	1-20	School education level and health status (physical, social and psychological) with a 6-year follow-up	Interaction between school education, physical health and cognitive performance. LSE highlights the decline of physical performance, due to age
12. Gitlin *et al.*[40] (2008)	319	≥70	G1: ≤8 G2: 9-11 G3: ≥12	Performance in daily living activities, after explanations on how to use tools, keep energy, safety, recovering from falls	Benefit vary according to school education level. Individuals with LSE benefit more from intervention, probably because they tend to have less Access to information
13. Tun e Lachman[29] (2008)	3616	32-85	G1: <16 G2: ≥16	Tasks of verbal reaction time alternating between sequences and inhibitory control	Individuals with LSE present worse performance and executive efficiency. Adults with superior education present performance similar to younger individuals with 10 years less school education
14. Brucki e Nitrini[11] (2008)	55 adults 27 elderly	G1:50-64 G2: ≥65	G1: IL (have never gone to school) G2: IL (have already gone to school) G3:1-4	Task of canceling figures (number of correctly canceled figures and visual search strategy)	L individuals present higher performance that IL ones, among IL, the ones who had already gone to school presented better performance
15. Neves[20] (2008)	42	≥60	G1: 1-7 G2: >7	Opposing fingers sequence (verification of learning and of transference of the skill for the other sequence, not trained)	The group with LSE does not transfer learning for the not trained sequence. The group with LSE performs a lower number of sequences per minute
16. Bramão *et al.*[21] (2007)	G1: 21 G2: 20	≥60	G1: IL G2: L	Switching a target presented on a screen, with the right or left index finger	IL individuals are slower to detect and switch targets, specially to the left
17. Camargos *et al.*[44] (2007)	2143	≥60	G1: ≤4 G2: ≥5	Getting dressed, taking a shower, using the toilet, laying down and getting up from bed, walking inside the house	Individuals with LSE present more functional difficulties and higher risk of functional difficulties during the last years of life
18. Jagger *et al.*[43] (2007)	13004	≥65	G1: 0-9 G2: 10-11 G3: ≥12	Capacity of mobility (going up and down stairs) and performing daily living activities (sitting down and getting up from a chair, putting shoes and socks on, preparing meals, walking outside the house, taking a shower)	Individuals with ISE present greater functional difficulties
19. Van der Elst *et al.*[25] (2006)	1856	24-81	G1: 1-7 G2: 8 G3: ≥9	Stroop test	Performance worsens with age and this worsening is more pronounced among individuals with LSE
20. Hester *et al.*[36] (2005)	363	60-89	G1: ≤11 G2: >11	Trail making test A (connecting numbers tracing a paper sheet) and B (connecting alternate letters and numbers)	Elderly individuals with LSE present more difficulty, specially in part B
21. Dansilio e Charamelo[15] (2005)	15 IL 15 A	≥60	G1: 0 G2: 6-7	Reproduce figures with drawings on a paper	Worst performance by individuals with LSE
22. Nitrini *et al.*[16] (2005)	745	≥65	G1: 0 G2: 1-3 G3: 4-7 G4: ≥8	Fist-edge-palm test (sequential manual movements)	Worst performance by individuals with LSE
23. Cavalcante[32] (2004)	60	≥60	1-10	Recognizing and performing several gestures	Individuals with LSE make more mistakes
24. Barnes *et al.*[38] (2004)	664	≥65	≤15 >15	Trail making test, Stroop test, mini exam of mental state (cognition/ executive function); North America Adult Reading Test (literacy)	Correlation between the performance in tests which assessed literacy and in cognitive and executive function tests
25. Nitrini *et al.*[9] (2004)	51	≥60	G1: IL G2: L	Clock test	LSE individuals make more mistakes
26. Tombaugh[37] (2004)	911	18-89	G1: ≤11 G2> 11	Trail making test	Worst performance by LSE individuals
27. Homann *et al.*[33] (2003)	187 healthy adults 200 with Parkinson's disease	30-85	G1: 8 G2: ≥9	Pushing alternate buttons on a computer keyboard as fast as possible, though without compromising accuracy	Elderly individuals with LSE presented slower speed in performing the movement of pushing buttons
28. Castro-Caldas *et al.*[2] (1998)	12	≥50	G1: L G2: IL	Task of words and pseudo words repetition and tomography with positron emission	In the repetition of words, the groups presented similar performance and brain activation patterns. IL have greater difficulty with pseudo words and they do not activate the same brain structures

A função executiva inclui uma série de habilidades, como a capacidade de resolução de problemas, inferência, alternância de tarefas, tomada de decisão, planejamento, sequenciamento, flexibilidade mental, entre outras, que estão no centro de diversas ações cotidianas e de vida diária. Inclui ainda atividades que exigem atenção em múltiplas tarefas, concomitantemente (Hanna-Pladdy, 2007; Coppin et al. 2006).

O processo natural do envelhecimento se torna ainda mais relevante diante do aparecimento de algumas doenças com maior incidência entre os idosos, como cardiovasculares e neurológicas. As doenças neurodegenerativas estão nesse grupo, entre elas, as mais comuns são a doença de Alzheimer e a DP. A DP não é incomum na população adulta, mas sua incidência aumenta na população idosa, afetando de 1,5 a 2% da população acima de 60 anos (Brienesse; Emerson, 2013). Em um estudo realizado com a população brasileira, esta porcentagem atingiu 3,4% da população acima de 64 anos. Descrita pela primeira vez em 1817 por James Parkinson (Blum et al., 2001; Parkinson, 1817), a condição é tipicamente caracterizada por distúrbios do sistema motor, sendo os principais sinais descritos o tremor de repouso, a rigidez muscular, a bradicinesia e a instabilidade postural (Jankovic, 2008).

Além dessa tétrade clássica, outros sintomas motores vêm sendo descritos como a bradicinesia, acinesia, diminuição de respostas adaptativas (como a força muscular) e redução da capacidade aeróbica (Brienesse; Emerson, 2013; Morris, 2000; Lima, 2013; Van der Kolk, 2013) e, com a progressão da doença é mais frequente a apresentação de distúrbio no equilíbrio postural, tanto em movimentos autoiniciados, como em movimentos compensatórios (Marchese, 2003; Yen, 2011) e na marcha, com apresentação de episódios de congelamento, durante a caminhada, chamado comumente de *freezing* (Morris et al., 2000).

Por muito tempo, idealizou-se que a doença atingiria somente o domínio motor. Entretanto, têm sido cada vez mais relatados déficits também em outros domínios (Brienesse; Emerson, 2013; Cruise et al., 2011), como dificuldade na interpretação e integração de sinais sensitivos, déficits no planejamento motor, alterações cognitivas e comportamentais, depressão, distúrbios no sono, entre outros (Kandel et al., 2012; Reijnders et al., 2009).

As alterações cognitivas presentes na DP, somadas aos déficits cognitivos característicos do envelhecimento, exacerbam as dificuldades e déficits funcionais desses indivíduos. Já é de conhecimento que pacientes com DP podem apresentar pior desempenho em testes de função executiva e que seu equilíbrio e marcha também são prejudicados quando associados a uma tarefa cognitiva concomitante (Souza et al., 2013; Marchese et al., 2003; Rochester et al., 2014).

Um teste bem reconhecido para a avaliação de função executiva é o *Trail Making Test* (TMT) (Tombaugh, 2004; Hester et al., 2005). Este teste é composto por duas partes, sendo que, em ambas, o paciente permanece sentado e utiliza um lápis ou caneta para realizar trilhas. Na parte A, o indivíduo é orientado a ligar os números de 1 a 25, dispostos aleatoriamente numa folha de papel de tamanho A4. Nessa parte, avalia-se a coordenação motora e a agilidade de escaneamento visual. Na segunda parte, o indivíduo deve ligar números de 1 a 12, intercalando-os com as letras do alfabeto, de A a L, de modo a obter a sequência 1-A-2-B...-12-L. Essa parte avalia, além das funções citadas anteriormente, a capacidade de alternância de tarefas, a atenção, a memória operacional e a flexibilidade mental (Voos, 2010).

Esse teste, além de avaliar especificamente diversos domínios das funções executivas, permite avaliar como o paciente com DP lida com atividades de dupla tarefa (motora e cognitiva). Há duas teorias que explicam o motivo pelo qual há prejuízo no desempenho motor e/ou cognitivo quando as duas atividades são realizadas ao mesmo tempo. A teoria do gargalo explica que, quando tarefas competem por recursos atentivos, o processamento central tem que priorizar uma em detrimento da outra (Pashler, 1994; Voos et al., 2015). Outra teoria, a dos múltiplos recursos de Wickens, defende que o prejuízo no desempenho das tarefas ocorre devido à baixa capacidade de processamento das informações, o que atrasa a interpretação de informações sensoriais e o processo de tomada de decisões (Voos et al. 2015).

Ambas as teorias podem explicar o prejuízo que pacientes com DP apresentam em tarefas duplas ou múltiplas. O atraso na interpretação de sinais aferentes e na tomada de decisão, somados à perda de automatização, decorrente da queda de dopamina nos núcleos da base, aumentam a necessidade atentiva em todas as tarefas, o que aumenta a necessidade de manter maior demanda cognitiva para executar tanto tarefas cognitivas quanto motoras (Bedeschi, 2013; Bloem et al., 2006). Por esse motivo alguns autores defendem que, frente a competição por recursos, há uma tendência de priorização das tarefas cognitivas, com prejuízo das tarefas motoras, como tamanho do passo e velocidade da marcha, por exemplo (Bloem et al., 2006; Yogev-Seligmann et al. 2002).

Nossa hipótese é que no TMT, idosos saudáveis apresentariam déficit na parte B (demanda cognitiva e motora), em comparação com a parte A (demanda motora). Por outro lado, pacientes com DP apresentariam pior desempenho já na parte A, porém esse prejuízo seria ainda mais acentuado na parte B, pelo aumento da demanda cognitiva.

Além disso, acreditamos que haja correlação entre a o desempenho no TMT (sobretudo na parte B para idosos saudáveis e em ambas as partes em pacientes com DP) e no teste de fluência verbal, uma vez que também a fluência verbal pode ser afetada pela diminuição da agilidade motora que afeta o restante do corpo, diminuindo assim a pontuação na fluência.

Ambos os testes são influenciados pela escolaridade (Souza et al., 2013; Brucki; Rocha, 2004). Entretanto, é possível que haja maior impacto desse aspecto nos indivíduos com DP, que apresentam menor reserva cognitiva e motora (Souza et al., 2013), do que nos idosos saudáveis.

2. OBJETIVOS

2.1 Objetivo Geral

O presente projeto tem como objetivo primário descrever dados normativos para o TMT para a população brasileira de pacientes com DP, comparando seu desempenho ao de idosos saudáveis.

2.2 Objetivos Específicos

Os objetivos específicos são:

- Verificar o efeito da escolaridade no desempenho do TMT, comparando se haveria influência da mesma maneira na população de idosos saudáveis e na população de pacientes com DP.

- Verificar se o desempenho no TMT pode estar correlacionado com o desempenho no teste de fluência verbal para ambas as populações, considerando que ambos são testes que envolvem dupla tarefa (destreza manual e processamento cognitivo no primeiro, e articulação fonatória e processamento cognitivo no segundo).

3. METODOLOGIA

3.1 Delineamento do Estudo

Será realizado um estudo observacional transversal.

3.2 Sujeitos

Para a formação do grupo de pacientes com DP, serão convidados os pacientes do grupo de Distúrbios do Movimento, do Departamento de Neurologia, do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. Todos os pacientes deverão ter o diagnóstico de DP, segundo os critérios diagnósticos da *United Kingdom Parkinson´s Disease Society Brain Bank* (Metman et al., 2004). O grupo de idosos saudáveis será composto por acompanhantes não consanguíneos de pacientes dos ambulatórios do Departamento de Neurologia da FMUSP, professores e alunos do departamento, integrantes da comunidade USP em geral. Os voluntários serão convidados por meio de cartazes, de anúncio no jornal da USP e de palestras em ambulatórios e cursos para a terceira idade, que são oferecidos pela universidade. Todos os voluntários deverão ler e assinar o termo de consentimento livre e esclarecido.

Os critérios de inclusão serão ter, no mínimo, quatro anos de educação formal, ter visão normal ou corrigida por lentes. Para o grupo de DP serão incluídos pacientes classificados pela escala de Hoehn and Yahr (HY) (Hoehn; Yahr, 1967) entre 2-3, com tratamento medicamentoso com dose estável e otimizada.

Os critérios de exclusão serão pontuação abaixo do escore padronizado na versão em português do Mini Exame do Estado Mental (MEEM) de acordo com a escolaridade (Brucki et al., 2003), indivíduos com menos de quatro anos de educação formal, pois não conseguem desempenhar o TMT (Yassuda et al., 2009), indivíduos com alguma doença cardiovascular, respiratória, neurológica, ortopédica, reumatológica, metabólica, ou psiquiátrica.

3.3 Procedimentos

Os voluntários serão triados de acordo com o MEEM (ANEXO 1). Pacientes com DP serão classificados de acordo com a escala de HY (ANEXO 2) e sua condição física avaliada será avaliada de acordo com a *Unified Parkinson´s Disease Rating Scale* (UPDRS), seção III (ANEXO 3). Serão registrados idade, escolaridade, tempo de duração da doença e presença de outras doenças associadas.

O MEEM tem sido utilizado em ambientes clínicos, para a triagem de declínio cognitivo, para o seguimento de quadros demenciais e no monitoramento de resposta ao tratamento. O ponto de corte 23/24 tem mostrado alta capacidade de discriminação de indivíduos cognitivamente alterados (Lourenço; Veras, 2006). O teste é composto por questões agrupadas em sete categorias. Cada categoria visa avaliar funções cognitivas específicas, como a orientação temporal, orientação espacial, repetição de três palavras, atenção e cálculo, recordação das três palavras, linguagem e capacidade construtiva visual. O escore do MEEM pode variar de zero a trinta, sendo trinta a melhor pontuação possível para capacidade cognitiva (Brucki et al., 2003).

A escala de HY é uma escala classificatória que gradua o nível de acometimento de pacientes com DP. Em ambientes de pesquisa, a HY é útil principalmente para a definição de critérios de inclusão/exclusão (figura 2). Pacientes com HY de 2-3 são considerados como moderadamente acometidos (Hoehn; Yahr, 1967).

A UPDRS avalia os sinais, sintomas e atividades funcionais dos pacientes, por meio do auto-relato e da observação clínica. É composta por 42 itens, divididos em quatro partes: atividade mental, comportamento e humor; atividades de vida diária; exploração motora e complicações da terapia medicamentosa. Nesse estudo, será utilizada apenas a seção III, que avalia os comprometimentos motores. Essa seção conta com 14 itens, sendo que a pontuação em cada item varia de 0 a 4. O valor máximo indica maior comprometimento pela doença e o valor mínimo indica normalidade (Goetz et al., 2008).

Após a triagem por essas escalas, todos os sujeitos, idosos saudáveis e pacientes com DP, realizarão o TMT (ANEXO 4) e o teste de fluência verbal (ANEXO 5).

O TMT será explicado ao voluntário e será oferecido treino prévio à avaliação, com uma versão simplificada de cada parte. No treino do TMT A, estarão dispostos no papel, oito círculos numerados de 1-8, que deverão ser ligados o mais rapidamente possível, sem que o sujeito retire a caneta do papel. Na parte A, o sujeito deverá seguir a mesma instrução, porém serão 25 círculos numerados e o tempo será cronometrado.

No treino da parte B, também estarão disponíveis oito círculos, quatro deles numerados de 1-4 e quatro deles com letras de A-D. Os círculos deverão ser conectados de maneira intercalada, em ordem crescente (1-A-2-B-3-C-4-D). A mesma instrução será dada para a realização da parte B, porém a sequência seguirá até 12-L. O teste será interrompido se não concluído em até 300 segundos, sendo essa a pontuação máxima possível para cada parte do teste.

A pontuação do teste será dada pelo tempo de realização do mesmo, sendo que o TMT A avaliará principalmente o componente motor da tarefa, o TMT B avaliará os componentes cognitivos e motores simultaneamente. Será extraída outra medida, o TMT delta, obtido pela subtração do TMT B do TMT A. O TMT delta será uma medida do componente cognitivo isolado, uma vez que eliminará o tempo gasto com o componente motor de ambas as tarefas (Voos, 2010).

Por fim, cada voluntário realizará o teste de fluência verbal. Também sentado, ele será solicitado a falar o máximo de palavras que se lembrar, em 60 segundos. O teste será aplicado de acordo com dois critérios: fonológico, no qual o indivíduo deve evocar palavras iniciadas com a letra F e critério semântico, no qual o indivíduo deve evocar nomes de frutas e nomes de animais. Palavras repetidas só serão pontuadas uma vez e não serão aceitos derivados da mesma palavra. No teste de fluência verbal com animais, serão pontuados, além do número total de palavras, as palavras faladas a cada quartil, nos 60 segundos, o número de categorias utilizadas (animais domésticos e da fazenda, selvagens, insetos, peixes, pássaros e répteis), a troca de categorias (sendo pelo menos três animais da mesma categoria) e o agrupamento (pelo menos três animais da mesma categoria) (Brucki; Rocha, 2004).

3.4 Análise Estatística

Todas as análises serão realizadas pelo software Statistica 12.0 para Windows (StatSoft, Inc, Tulsa, OK), sendo que será adotado nível de significância alfa < 0.05.

Os grupos DP e IS serão comparados em termos da idade e escolaridade por meio do teste t de Student e as diferenças de gênero serão pesquisadas por meio do teste qui-quadrado. Além disso, o desempenho dos grupos (idosos saudáveis e pacientes com DP) no TMT A, TMT B e TMT delta, assim como nos teste de fluência, serão comparados utilizando testes de Análise de Variância (ANOVAs). Da mesma maneira, a ANOVA será utilizada para verificar o efeito da escolaridade no TMT, para cada grupo.

Por fim, será aplicado o teste de correlação de Pearson, para investigar possíveis relações entre o desempenho nos testes de fluência e no TMT, para ambos os grupos separadamente.

4. REFERÊNCIAS BIBLIOGRÁFICAS

Acevedo A, Loewenstein DA, Barker WW, Harwood DG, Luis C, Bravo M, Hurwitz DA, Aguero H, Greenfield L, Duara R. Category fluency test: normative data for English- and Spanish- speaking elderly. *Journal of the International Neuropsychological Society*. 2000;6(7):760-9.

Araujo NB, Barca ML, Engedal K, Coutinho ESF, Deslandes AC, Laks J. Verbal fluency in Alzheimer’s disease, Parkinson’s disease, and major depression. *Clinics*. 2011;66(4):623-7.

Bedeschi C. *Treino de Marcha com Demandas Motoras e Cognitivas Integradas em um Contexto Funcional em Pacientes com Doença de Parkinson* [Tese]. São Paulo: Instituto de Psicologia da Universidade de São Paulo; 2013.

Bloem BR, Grimbergen YA, van Dijk JG, Munneke M. The ‘‘posture second’’ strategy: a review of wrong priorities in Parkinson’s disease. *J Neurol Sci*. 2006:248(1-2):196-204.

Blum D, Torch S, Lambeng N, Nissou M, Benabid AL, Sadoul R, Verna JM. Molecular pathways involved in the neurotoxicity of 6-OHDA, dopamine and MPTP: contribution to the apoptotic theory in Parkinson's disease. *Progress in Neurobiology*. 2001:65(2)135-72.

Brienesse LA, Emerson MN. Effects of Resistance Training for people with Parkinson’s disease: a systematic review. *JAMA*. 2013;14(4):236-41

Brucki SMD, Nitrini R, Caramelli P, Bertolucci PH, Okamoto IH. Sugestões para o uso do mini-exame do estado mental no Brasil. *Arq Neuropsiquiatr*. 2003;61(3B):777–81.

Brucki SMD, Rocha MSG. Category fluency test: Effects of age, gender and education on total scores, clustering and switching in Brazilian Portuguese-speaking subjects. *Braz J Med Biol Res*. 2004; 37(12):1771-7.

Carvalho JAM, Rodríguez-Wong LL. A transição da estrutura etária da população brasileira na primeira metade do século XXI. *Cadernos de Saúde Pública.* 2008;24(3):597-605.

Coppin AK, Shumway-Cook A, Saczynski J, Patel KV, Ble A, Ferrucci L, Guralnik JM. Association of executive function and performance of dual-task physical tests among older adults: analyses from the InChianti study. *Age and Ageing*. 2006;35(6):619-24.

Cruise KE, Bucks RS, Loftus AM, Newton RU, Pegoraro R, Thomas MG. Exercise and Parkinson’s: Benefits for cognition and quality of life. *J Ambulation*. 2011;123(1):13-19.

DeVita P, Hortobagyi T. Age increases the skeletal versus muscular component of lower extremity stiffness during stepping down. J Gerontol A Biol Sci Med Sci. 2000;55(12):B593-600.

Gavin TP, Kraus RM, Carrithers JA, Garry JP, Hickner RC. Aging and the Skeletal Muscle Angiogenic Response to Exercise in Women. *J Gerontol A Biol Sci Med Sci*. 2014(2).pii:glu138.[Epub ahead of print].

Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N. Movement disorder society-sponsored revision of the unified parkinson’s disease rating scale (mds-updrs): Scale presentation and clinimetric testing results. *Mov Disord*. 2008;23(15):2129-70.

Hanna-Pladdy B. Dysexecutive Syndromes in Neurologic Disease. *Journal of Neurological Physical Therapy.* 2007;31(3):119-127.

Henry JD, Crawford JR. Verbal fluency deficits in Parkinson ’ s disease : A meta-analysis. *J Int Neuropsychol Soc*. 2004;10(4):608-22.

Hester RL, Kinsella GJ, Ong B, McGregor J. Demographic influences on baseline and derived scores from the trail making test in healthy older Australian adults. *Clin Neuropsychol.* 2005;19(1):45–54.

Hoehn MM, Yahr MD. Parkinsonism-onset progression and mortality. *Neurology*. 1967;17(5):427-42.

Jankovic J. Parkinson´s Disease: Clinical Features and Diagnosis. *Journal of Neurology, Neurosurgery & Psychiatry*. 2008;79:368-76.

Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA, Hudspeth AJ. Principles of neural science. 5th ed. Nova Yorque: McGraw-Hill; 2012.

Kempler D, Teng EL, Dick M, Taussig M, Davis DS. The effects of age, education, and ethnicity on verbal fluency. *Journal of the International Neuropsychological Society*. 1998;4(6):531-8.

Kherad M, Mellström D, Rosengren BE, Hasserius R, Nilsson JÅ, Redlund-Johnell I, Ohlsson C, Lorentzon M, Karlsson MK. The number and characteristics of prevalent vertebral fractures in elderly men are associated with low bone mass and osteoporosis. *Bone Joint J.* 2015;97(8):1106-10.

Lima A, Scianni F, Rodrigues-de-Paula F. Progressive resistance exercise improves strength and physical performance in people with mild to moderate Parkinson's disease: a systematic review. *Journal of physiotherapy*. 2013;59(1):7-13.

Lourenço RA, Veras RP. Mini-Exame do Estado Mental: características psicométricas em idosos ambulatoriais. *Rev Saúde Pública.* 2006;40(4):712-9.

Marchese R, Bove M, Abruzzese G.Effect of cognitive and motor tasks on postural stability in Parkinson's disease: A posturographic study. *Movement Disorders*. 2003;18(6):652-8.

Masaki M, Ikezoe T, Fukumoto Y, Minami S, Tsukagoshi R, Sakuma K, Ibuki S, Yamada Y, Kimura M, Ichihashi N. Association of sagittal spinal alignment with thickness and echo intensity of lumbar back muscles in middle-aged and elderly women. *Arch Gerontol Geriatr.* 2015 Sep-Oct;61(2):197-201

Metman LV, Myre B, Verwey N, Hassin-Baer S, Arzbaecher J, Sierens D, Bakay R. Test-retest reliability of UPDRS- III, dyskinesia scales, and timed motor test in patients with advanced Parkinson's disease: an argument against multiple baseline assessments. *Mov Disord*. 2004;19(9):1079–84.

Morris ME. Movement disorders in people with Parkinson diseas: a model for physical therapy. *Physical Therapy*. 2000;80(6):578-597.

Parkinson J. An essay on the shaking palsy. (1817). *The journal of neuropsychiatry and clinical neurosciences*. 2002;14(2):223-36.

Pashler H. Dual-task interference in simple tasks: data and theory. *Psychology Bulletin*. 1994;116(2):220-44 .

Reijnders JSM, Ehrt U, Lousberg R, Aarsland D, Leentjens AFG. The association between motor subtypes and pshychopathology in Parkinson's disease. *Parkinsonism & related disorders*. 2009;15(5):379-82.

Rochester L, Galna B, Lord S, Burn D. The nature of dual-task interference during gait in incident Parkinson's disease. *Neuroscience.* 2014;265:83-94.

Souza CO, Voos MC, Francato DV, Chien H F, Barbosa ER. Influence of educational status on executive function and functional balance in individuals with Parkinson disease. *Cognitive and Behavioral neurology*. 2013;26(1):6-13.

Tombaugh TN. TrailMaking Test A and B: Normative data stratified by age and education. *Arch Clin Neuropsychol.* 2004;19(2):203–214.

Van der Kolk NM, King L. Effects of exercise on mobility in people with Parkinson's disease. *Movement Disorders.* 2013;28(11):1587-96.

Voos MC, Custódio EB, Malaquias J. Relationship of executive function and educational status with functional balance in older adults. J Geriatr Phys Ther. 2011;34(1):11-8.

Voos MC, Mansur LL, Caromano FA, Brucki SMD, Valle LER. The influence of educational status on motor performance and learning: a literature review. *Fisioterapia & Pesquisa*. 2014;21(3):297-304.

Voos MC, Piemonte MEP, Castelli LZ, Machado MSA, Teixeira PPS, Caromano FA. Association between educacional status and dual-task performance in Young adults. *Percept Mot Skills.* 2015;120(2):417-437.

Voos MC. *A influência da idade e da escolaridade na execução e no aprendizado de uma tarefa cognitivo-motora* [Tese]. São Paulo: Instituto de Psicologia da Universidade de São Paulo; 2010.

Yassuda M, Diniz BSO, Flaks MK, Viola LF, Pereira FS, Nunes PV, Forlenza OV. Neuropsychological profile of Brazilian older adults with heterogeneous educational backgrounds. Arch Clin Neuropsychol. 2009;24(1):71-9.

Yen C, Kwan L, Ming H. Effects of virtual reality augmented balance training on sensory organization and attentional demand for postural control in people with Parkinson disease: A randomized controlled trial. Physical Therapy. 2011;91(6):862-74.

Yogev-Seligmann G, Rotem-Galili Y, Dickstein R, Giladi N, Hausdorff JM. Effects os explicit prioritization on dual task walking in Patients with Parkinson's Disease. Gait Posture. 2012:35(4):641-6.

ANEXO 7 – Resumo apresentado no 20th *International Congress of Parkinson's disease and Movement Disorders*e publicado na Revista*Movement Disorders*

EXECUTIVE FUNCTION AND VERBAL FLUENCY IN PATIENTS WITH PARKINSON'S DISEASE

A.F. Barbosa, M.C. Voos, C.O. Souza, J. Chen, H.F. Chien, D.V. Francato, E.R. Barbosa, L.L. Mansur

Objective: To determine whether the phonemic verbal fluency test is a purely cognitive measure or involves cognitive-motor interaction, if related to TMT.

Background: Two of the most used tests in clinical evaluation and scientific studies with PD patients are the Trail Making Test (TMT) and the VF. However, these tests are frequently interpreted as only providing executive function measures. Few studies consider them as cognitive-motor measures. Therefore, the motor component, which may be impaired, is overlooked. For TMT some extrapolations have been carried out, because part A involves mainly motor aspects and part B adds cognitive overload. The delta (part B – part A) isolates the cognitive performance. In the interpretation of VF, motor aspects are not considered. Therefore, a motor dysfunction (due to bradykinesia of phonoarticulatory muscles) can be interpreted as cognitive impairment.

Methods: Forty patients diagnosed with PD (Hoehn & Yahr 2-3) from the Movement Disorders clinic at the Hospital das Clinicas and twenty-seven healthy elderly controls participated. They had normal performance on Mini Mental State Examination (score above 24). Groups were similar in age and education. Evaluation consisted of TMT and phonemic VF. As the groups showed non-normal distribution, Spearman correlation tests were used to test relations between the variables for both groups separately. Significance level was set at alfa<0.05.

Results: Table 1 shows the correlations between VF and TMT. The scatterplots in figures 1 and 2 show the performance on part B and VF of both groups Spearman correlation tests results for both groups. Healthy elderlies showed less variability in TMT performance. As manual dexterity and executive function are not affected in this group, no correlation was found. Considering the PD patients, the ones with higher cognitive reserve (as evidenced by faster performance on part B of TMT) also show less severe clinical manifestation of PD (assessed by part A of TMT). It is noted in the table, that VF and part B of TMT have strong correlation. The correlation between part A of TMT (motor performance) and phonemic VF was stronger correlation than the correlation between the delta (cognitive component) and VF.

Conclusions: Verbal fluency is a cognitive-motor test and, in PD patients, the interpretation of results as only cognitive assessment should be done with caution.

Tabela 1

Spearman correlation tests results for both groups			
Phonemic fluency test	**TMT A**	**TMT B**	**TMT delta**
PD patients	-0,631	-0,733	-0,481
Healthy elderlies	-0,185	-0,249	-0,249

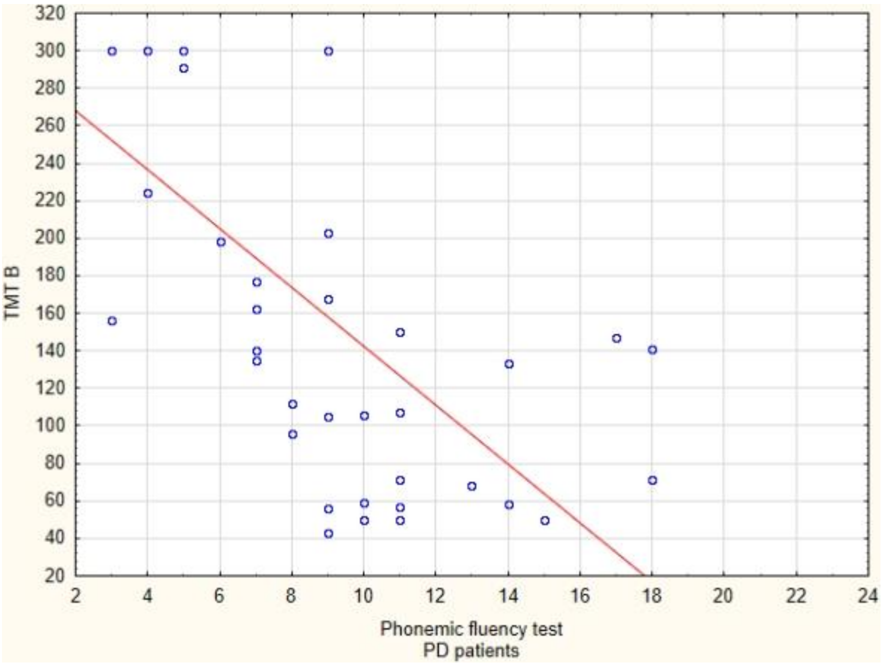


Figure 1

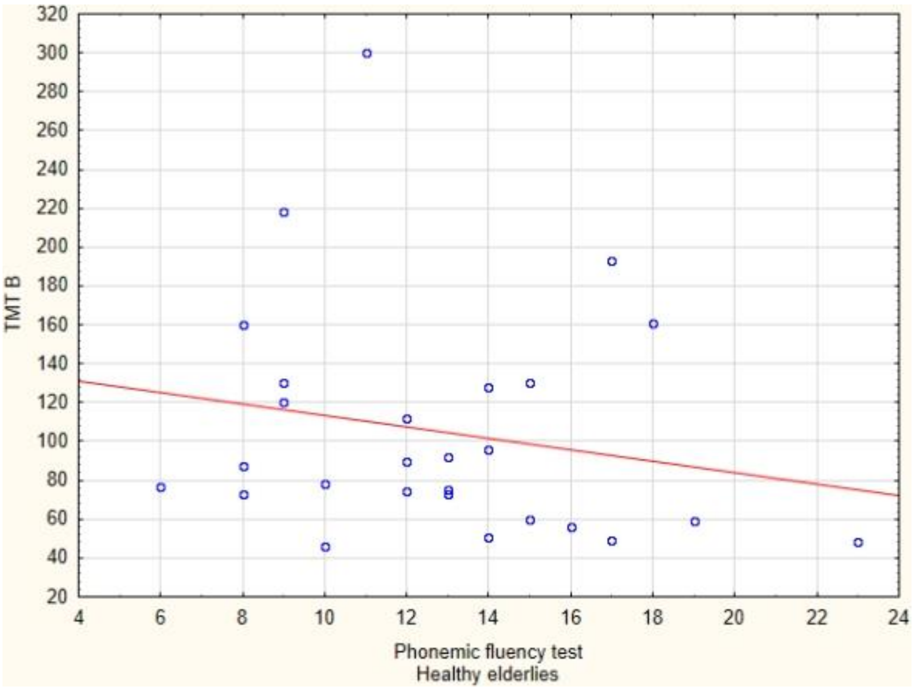
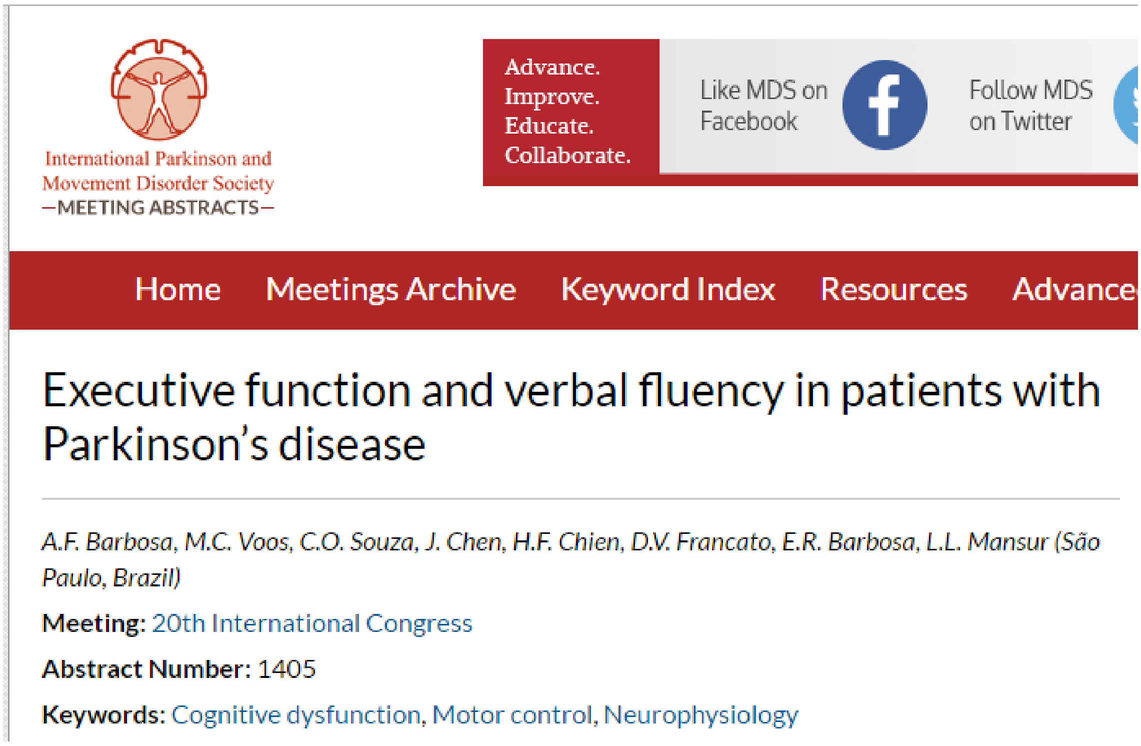


Figure 2



International Parkinson and Movement Disorder Society
—MEETING ABSTRACTS—

Advance. Improve. Educate. Collaborate.

Like MDS on Facebook

Follow MDS on Twitter

Home Meetings Archive Keyword Index Resources Advance

Executive function and verbal fluency in patients with Parkinson's disease

A.F. Barbosa, M.C. Voos, C.O. Souza, J. Chen, H.F. Chien, D.V. Francato, E.R. Barbosa, L.L. Mansur (São Paulo, Brazil)

Meeting: 20th International Congress

Abstract Number: 1405

Keywords: Cognitive dysfunction, Motor control, Neurophysiology

Detalhe da publicação no site da Movement Disorder Society

ANEXO 8 – Resumo apresentado no XXVII Congresso Brasileiro de Neurologia

PERFORMANCE OF PATIENTS WITH PARKINSON'S DISEASE ON TRAIL MAKING TEST: PRELIMINARY RESULTS OF NORMATIVE DATA

Alessandra F. Barbosa[1] MSc student; Carolina O. Souza[2] MSc; Hsin. F. Chien[2] PhD; Janini Chen[2] PT; Débora V. Francato[2] PT; Egberto R. Barbosa[2] PhD; Letícia L. Mansur PhD[1]; Mariana C. Voos[1] PhD.

1. Physical Therapy, Occupational Therapy and Speech Therapy Department, University of São Paulo School of Medicine, São Paulo, Brazil.

2. Movement Disorders Clinic, Department of Neurology, Hospital das Clínicas of the University of São Paulo School of Medicine, São Paulo, Brazil.

Background: One of the most common non-motor impairment in Parkinson´s Disease (PD) patients is executive dysfunction. Trail Making Test (TMT) is widely used for executive function assessment. Studies described normative data of TMT for middle-aged/ older adults and showed that TMT is influenced by age and education. However, there is not enough data of PD patients and it is unknown if age and education would have the same impact on them.

Aim: To describe and compare the performance of PD patients and healthy controls (with paired age and education) on TMT, to test the relationship between the performance on TMT and Hoehn & Yahr (H&Y), age and education.

Methods: Fifty-six patients diagnosed with PD (H&Y: 2-3) and 66 controls were evaluated. TMT is a paper and pencil test and consists on connecting numbers (Part A) and alternated numbers and letters (Part B). TMT delta is the time on Part B minus the time on Part A. Descriptive statistics were performed to characterize the groups according to demographic data and the performance on TMT. Spearman correlation tests investigated the relationships between TMT times, age, education and H&Y. PD and control groups were divided in three subgroups, according to the number of years of education (low: 4-8; medium: 9-11; high: 12 or more years). The performances of PD and control groups were compared for each subgroup with ANOVAs. Significance level was alfa<0.05.

Results: In PD group, times on TMT A ranged from 17 to 281 seconds (mean: 68.8; SD: 53.6 seconds). In control group, times ranged from 16 to 117 seconds (mean: 41.2; SD: 17.6 seconds). In PD group, the moderately correlations were TMT A with age and education; TMT B with age, education and H&Y; TMT delta with education. In control group, the moderately correlations were TMT B and TMT delta with age. There were also some weakly correlations between these parameters. ANOVA showed significant differences between the performances of PD and control groups in low (p=0.020) and medium education (p=0.001) groups, but not in the high education group (p=0.370).

Conclusion: PD patients had longer and more variable times in both TMT parts. In addition, performance was related to age and education. However, the effect of education may be higher on PD than on control groups. TMT performance was related to PD severity (H&Y). Normative data have great importance for application and interpretation of TMT in PD patients.

ANEXO 9 – Resumo apresentado na 7ª Reunião do Departamento Científico de Transtornos do Movimento da Academia Brasileira de Neurologia

COGNITIVE OR COGNITIVE-MOTOR EXECUTIVE FUNCTION TASKS? EVALUATING VERBAL FLUENCY MEASURES IN PATIENTS WITH PARKINSON DISEASE

Alessandra Ferreira Barbosa[1,2]; Mariana Callil Voos[1,2]; Janini Chen[2,3]; Debora Cristina Valente Francato[2,3]; Carolina de Oliveira Souza[2,3]; Egberto Reis Barbosa[3]; Hsin Fen Chien[2,3]; Letícia Lessa Mansur[1]

1. Physical Therapy, Occupational Therapy and Speech Therapy Department, University of São Paulo, Faculty of Medicine, São Paulo, Brazil.
2. ReMove. Rehabilitation in Movement Disorders Research Group.
3. Movement Disorders Clinic, Department of Neurology, Clinics Hospital of University of São Paulo, Faculty of Medicine, São Paulo, Brazil.

Introduction: Executive function deficits are observed in patients with Parkinson disease (PD) since early stages and have great impact on daily live activities. Several tests are indicated to the executive function assessment. However it is not clear if the results are related to the motor or cognitive component involved in the tasks.

Objective: This study aimed to describe the performance of patients with PD and an age- and education-matched control group on phonemic/semantic verbal fluency, oral diadochokinesia and executive function tests and to investigate possible relationships between these measures.

Methods: This study was approved by the Committee on Research Ethics at Clinics Hospital of University of São Paulo (process 1.631.497) and all participants read and signed the written informed consent. Forty patients with PD and forty controls were evaluated with Trail Making Test (executive function), phonemic/semantic verbal fluency and oral diadochokinesia (/pataka/, a motor evaluation of the language production) tests. Data showed normal distribution (tested by Kolmogorov-Smirnov)

and the groups were compared by ANOVA and relationships were investigated by Pearson tests.

Results: The groups did not significantly differ in age, gender, years of formal education and Mini-mental State Examination scores. ANOVA showed significant differences between groups ($F_{1,78}$=12.98; p<0.001) and fluency tests (phonemic or semantic) ($F_{1,78}$=81.23; p<0.001), but no interaction between groups and tests (($F_{1,78}$=0.84; p=0.772). Post hoc Tukey tests showed that patients with PD said less words than controls in both fluency tests (p<0.001). Patients with PD said less syllables per second in the diadochokinesia test ($F_{1,23}$=6.36; p=0.019) and showed longer times in TMT parts A and B. ANOVA showed significant differences between TMT parts ($F_{1,78}$=154.02; p<0.001). Part B showed longer times than part A. No interaction between groups and parts was observed ($F_{1,78}$=0.20; p=0.652). TMT delta did not significantly differ between the groups (p=0.855). Oral diadochokinesia strongly correlated to TMT (parts A and B) and to phonemic verbal fluency (Table 1).

Conclusion: PD patients performed poorly in the executive function tests. However, it is important to consider the cognitive and motor impact on the results of all tests. Oral diadochokinesia involves not only phonoarticulatory coordination but also response inhibition and phonological processes. The motor aspects of verbal fluency should be considered not to overestimate the cognitive impairment of patients with PD. Cognitive-motor interaction must be considered in tests that require phonoarticulatory coordination, hand dexterity and verbal fluency in PD patients.

Table 1: Correlations between TMT, semantic and phonemic verbal fluency and oral diadochokinesia scores in patients with Parkinson disease (Pearson correlations coefficients).

	Part A (TMT)	**Part B (TMT)**	**TMT delta**	**Oral diadochokinesia**
Semantic verbal fluency test	r= -0.311 p= 0.325	r= -0.468 p= 0.125	r= -0.339 p= 0.281	r= 0.325 p= 0.303
Phonemic verbal fluency test	**r= -0.712 p= 0.009***	**r= -0.874 p= 0.001***	**r= -0.740 p= 0.006***	**r= 0.684 p= 0.014***
Oral diadochokinesia	**r= -0.838 p= 0.001***	**r= -0.824 p= 0.001***	**r= -0.689 p= 0.013***	-----

ANEXO 10 – Comprovante de aceite do Artigo à revista *BioMed Research International*

Gmail Alessandra Barbosa <alefbar@gmail.com>

7893975: Your manuscript has been accepted
1 mensagem

Pablo Mir <bmri@hindawi.com> 18 de julho de 2017 09:11
Responder a: ramy.tarek@hindawi.com
Para: ftmarivoos@gmail.com
Cc: pmir@us.es, alefbar@gmail.com, janinichen@gmail.com, valente.debora@hotmail.com, souzaco@ig.com.br, egbertob@8415.com.br, chien.74@fmusp.org.br, lmansur@usp.br

Dear Dr. Voos,

The review process of Research Article 7893975 titled "Cognitive or cognitive-motor executive function tasks? Evaluating verbal fluency measures in patients with Parkinson disease" by Alessandra Barbosa, Mariana Voos, Janini Chen, Débora Francato, Carolina Souza, Egberto Reis Barbosa, Hsin Fen Chien and Leticia Mansur submitted to BioMed Research International has been completed. I am pleased to inform you that your manuscript has now been accepted for publication in the journal.

The publication process of your manuscript will be initiated upon the receipt of electronic files. Please log in to the Manuscript Tracking System at the link below using your username and password, and upload the electronic files of your final accepted version within the next 2-3 days.

http://mts.hindawi.com/author/7893975/upload.files/

The electronic files should include the following:

1- Source file of the final accepted manuscript (Word or TeX/LaTeX).
2- PDF file of the final accepted manuscript.
3- Editable figure files (each figure in a separate EPS/PostScript/Word file) if any, taking into consideration that TIFF, JPG, JPEG, BMP formats are not editable.

Thank you again for submitting your manuscript to BioMed Research International.

Best regards,

Pablo Mir